Dissertation on

AN OBSERVATIONAL STUDY TO DETERMINE THE ROLE OF SEPTICEMIA IN RETINOPATHY OF PREMATURITY AMONG PRETERM BABIES

Submitted in partial fulfillment of requirements of

M.S. DEGREE

BRANCH –III (OPHTHALMOLOGY)

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MADURAI MEDICAL COLLEGE

MADURAI

The Tamilnadu Dr.M.G.R. Medical University

CHENNAI, TAMILNADU

MAY, 2019

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This is to certify that this dissertation entitled **AN OBSERVATIONAL STUDY TO DETERMINE THE ROLE OF SEPTICEMIA IN RETINOPATHY OF PREMATURITY AMONG PRETERM BABIES"** is a bonafide record of research work done by **Dr.M.SUHANYA,** Post Graduate Resident in Department of Ophthalmology, Madurai Medical College, Madurai.

She has submitted this in partial fulfillment of the regulations laid down by The Tamil Nadu Dr. M.G.R. Medical University, for the award of Master of Surgery Degree Branch III (Ophthalmology), under our guidance and supervision during the academic years 2016-2019.

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This is to certify that this dissertation entitled **"AN OBSERVATIONAL STUDY TO DETERMINE THE ROLE OF SEPTICEMIA IN RETINOPATHY OF PREMATURITY AMONG PRETERM BABIES"** is a bonafide record of research work done by **Dr.M.SUHANYA,** Post Graduate Resident in Department of Ophthalmology, Madurai Medical College, Madurai.

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DECLARATION

I, **Dr. M.SUHANYA** hereby solemnly declare that, this dissertation **"AN OBSERVATIONAL STUDY TO DETERMINE THE ROLE OF SEPTICEMIA IN RETINOPATHY OF PREMATURITY AMONG PRETERM BABIES"** was done by me.

I also declare that this bonafide work / a part of this work was not submitted by me / anyone else, for any award, for Degree / Diploma to any other University / Board either in India / abroad. This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfilment of the rules and regulations for the award of Master of Surgery degree Branch -III (Ophthalmology) to be held in May 2019.

Place: Madurai (Dr. M.SUHANYA)

Date:

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CERTIFICATE - II

This is to certify that this dissertation work titled "**AN OBSERVATIONAL STUDY TO DETERMINE THE ROLE OF SEPTICEMIA IN RETINOPATHY OF PREMATURITY AMONG PRETERM INFANTS"** of the candidate **Dr.M.SUHANYA** with registration Number **221613106** for the award of **MASTER OF SURGERY** in the branch of **OPHTHALMOLOGY(BRANCH III)** . I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **13%** percentage of plagiarism in the dissertation.

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INDEX

ANNEXURES

PART ONE

INTRODUCTION:

Retinopathy of Prematurity (ROP) is a retinal disorder affecting the developing vessels of premature infants.ROP being a preventable childhood blindness, it mainly affects 38% –51.9 % in low birth weight babies.

Normally, retinal vasculature develops in relative hypoxic state. When this environment is disturbed, ROP sets in. The classical risk factors for ROP is low birth weight, low gestational weight, fluctuation in oxygen supply. Hence mainstay of treatment is focussed on stability in oxygen supplementation.

Despite such efforts the incidence of ROP continues to rise. This is likely because of increased NICU facilities leading to increased survival rates of preterm infants. During their survival period, babies are exposed to various insults or in either way survive with the insults exposed prenatally. Both of which can result in ROP.

The major pathological process of ROP is due to incomplete peripheral vascularisation of retina at birth in preterm babies.

ROP remains latent for a month from the birth to occur as the vessel growth needs IGF and thereafter showing its progression .Hence timely interventions is needed to avoid irreversible blindness.

By revised ET-ROP study, nearly 8% of screened babies warrants treatment depending upon current ROP screening guidelines. Whereas more than 90% of screened babies either requires no treatment or they never develops ROP.

Even if the present ablation treatment reduces the incidence of childhood blindness among babies who have severe ROP, they still end up with visual impairment which has significant impact on development of the eye .As a result of which the baby would develop global developmental delay.

Apart from the three classical risk factors of ROP, there are other factors that may induce ROP. Those factors can be sepsis, thrombocytopenia, poor postnatal weight gain, blood transfusion, use of surfactants.

SEPSIS:

Sepsis has both direct and indirect effect on retina.

DIRECT EFFECT:

Infectious organisms or their metabolic products induces production of proinflammatory cytokines such as IL-6,IL-8 and TNF- alpha which affects vascular endothelial cells resulting in VEGF production.

INDIRECT EFFECT:

Newborns in sepsis are at high risk of circulatory and respiratory insufficiency. These hypotension and fluctuation of oxygen saturation affects retinal perfusion.

NEONATAL SEPSIS:

Neonatal sepsis or sepsis neonatorum when pathogenic organism gain access into the blood stream. It occurs in infants of age less than 90 days.

According to National Neonatal Perinatal Database, 20% neonates develop sepsis. Sepsis can manifest as clinical syndrome with or without bacteremia.

It may present as

-Septicemia

-Meningitis

-Pneumonia

-Arthritis

-Osteomyelitis

- Urinary tract infection.

The most common organisms associated with sepsis are Klebsiella, Staphylococcus aureus, Pseudomonas species.

Sepsis can be approached as

-Early Onset Sepsis(EOS)

-Late onset sepsis(LOS)

EARLY ONSET SEPSIS:

Sepsis occurs within 72 hours of birth .The course of presentation is Fulminant and multisystem involvement is seen. Most common presentation of EOS is respiratory distress or pneumonia. In EOS, the source of infection is

mainly from maternal genital tract.

The following factors increases the risk of EOS in infants

-Maternal infection with group B streptococcus during the pregnancy.

-Infection of amniotic fluid and the placental tissue.

-Multiple pervaginal examinations.

-Maternal fever and examination

LATE ONSET SEPSIS:

Sepsis occurs after 72 hours of birth. It commonly presents as septicaemia, meningitis, pneumonia. The course of presentation is slow progressive and focal. The most common presentation is meningitis. It can be hospital acquired or community based. LOS can be due to lack of breast feedings, prelacteal feeds, bottle feed, poor hygiene or cord care, low birth weight, prematurity, mechanical ventilation, central line, long hospital stay and superficial infections such as umbilical sepsis ,pyoderma,etc.,

Organisms which are commonly implicated in causing late onset sepsis are

-Coagulase negative staphylococcus (CONS)

- staphylococcus aureus

-E.coli

-Klebsiella

-Pseudomonas

-Enterobacter

-Candida

-Serratia

- Acinetobacter

-Anaerobes

CLINICAL FEATURES OF SEPSIS:

SUBTLE OR EARLIEST SIGN:

-Hypothermia(most common)/ Hyperthermia

-Lethargy, poor cry, refusal to suck

-Poor perfusion detected by prolonged capillary refill time

-Bradycardia or Tachycardia.

-Hypoglycemia or hyperglycemia

-Hypotonia

SIGNS OF CIRCULATORY SYSTEM:

Pallor, cyanosis ,cold ,clammy skin ,oedema, hypotension , bradycardia or tachycardia.

SIGNS OF RESPIRATORY SYSTEM:

Irregular respiration, apnea, dyspnea, Grunting ,retraction and cyanosis

SIGNS OF CENTRAL NERVOUS SYSTEM:

Signs of poor activity such as lethargy, coma, poor cry , irritability, tremors, full fontanel.

SIGNS OF GASTROINTESTINAL SYSTEM:

Poor feeding, vomiting, diarrhoea or decreased passage of stools, abdominal distension and hepatomegaly.

SIGNS OF HAEMATOPOEITIC SYSTEM:

Jaundice, pallor, ecchymosis, splenomegaly and bleeding.

SIGNS INVOLVING SKIN:

Rashes, purpura and pustules.

Neonatal sepsis is clinically defined by Systemic inflammatory Response Syndrome (SIRS) as when 2 or more of the following conditions are present.

- Temperature instability < 35c and > 38.5c
- Hypoxemia (Pao2 <70 mmHg on room air).
- Tachypnoea and tachycardia >2SD for the mean age.
- Delayed capillary refill >3sec.
- Hypotension >2SD below the mean for age.
- Oliguria (Urine output <0.5 ml/kg/hr)
- Altered mental status.
- Lactic acidosis(elevated plasma lacate or arterial PH <7.25)

Sepsis is confirmed by sepsis screen and 2 blood cultures taken at two different sites at same time shows growth of organisms.

SEPSIS SCREEN:

It is done when babies are clinically suspected to have sepsis. When two of the following criterias are said to be positive, sepsis screen is said to be positive.

- Total leukocyte count < 5000/mm3.
- Absolute neutrophil count <1800
- Immature / Total neutrophil count >/= 0.2
- ESR > 15mm in first hour
- CRP >1mg/dl

MANAGEMENT OF SEPSIS:

It includes

- Supportive care and
- Antibiotic therapy

SUPPORTIVE CARE:

- Warmth should be provided.
- I.V fluids(normal saline)10mg/kg is administered if CRT >3 sec.
- 10% glucose, 2ml/kg stat over 2-3 minutes to manage hypoglycaemia.
- Vitamin K 1mg im to prevent bleeding
- Oxygen hood or mask if the baby has cyanosis or grunting
- In case of apnoea physical stimulation followed by bag and mask ventilation given.

- If baby is sick oral feed is avoided and intravenous fluid is given.
- If baby suffer from sclerema, exchange transfusion with fresh whole blood may be required.

ANTIBIOTIC THERAPY:

Antibiotic regime should cover common causative organism like E.coli, staphyloccus aureus and klebsiella pneumonia. A combination of gentamycin and ampicillin (penicillin and aminoglycoside)is recommended for the treatment of sepsis.

- Injection Ampicillin 50mg/kg/dose 12^{th} hourly iv or im for 7-10 days
- Injection Gentamycin 2.5mg/kg/dose BD IV/IM for 7-10 days.

TREATMENT OF SUPERFICIAL INFECTIONS:

- In case of pustules, incision and drainage in severe cases followed by betadine wash and locally antibiotic is applied over the wound.
- For conjunctivitis antibiotic eye drop is instilled.
- Oral thrush can be treated by local application of nystatin or clotrimazole

HISTORY:

ROP was first reported by Terry in 1942 in AJO ("American journal of Ophthalmology"). The name"Retrolental fibroplasias" was framed by Dr.Harry Messenger. Earlier it was believed that ROP is due to persistence of hyaloid artery behind the lens and the tunica vasculosa lentis . This belief was later disproved by Owens and Owens. They analysed a case series of retrolental fibroplasias and they found out that the etiology of the disease was not due to persistent hyaloid system congenitally. They suggested the pathogenesis would occur posnatally.

In 1950, Multicentre randomized clinical trial was conducted by National Cooperative Study which proposed the association of ROP and supplemental oxygen. This Study proved that the reducing the oxygen supplementation in NICU leads to drop in incidence of ROP. But reducing the supplementation of oxygen led to increased morbidity and mortality among premature infants.

In 1970s, the concentration of oxygen delivered to the babies was individualised, titrated and monitored using arterial blood gas.This helped greatly to decrease ROP incidence and also to increases the survivability of the babies.

In 1980, incidence of ROP had begun to rise as survival rate of the preterm babies started to rise with advancing care facilities in NICU.

INCIDENCE AND PREVALENCE:

In India, incidence of ROP ranges 38-52% among low birth weight babies. Annual live births in India is around 26 million, 9 % of whose birth weight falls under <2000 grams. This implies that almost 2 million newborns are under risk to develope ROP. Incidence of ROP among babies with BW of <750gms is 90%. As the BW increases, incidence of ROP decreases. ROP is seen in 80 to 90 % of low birth weight babies who had been treated with oxygen supplementation.

Also, the ROP incidence with low gestational age of 24-27 weeks is 89 %. With increasing gestational age , incidence of ROP decreases.

This table depicts the incidence of ROP and severity of ROP in premature babies with birth weight less than or equal to1,251 grams.

PREVIOUS STUDIES	No.of babies	Any ROP (%)	Prethreshold ROP (%)	Threshold ROP (%)
CRYO-ROP STUDY	4,099	66	18	6
LIGHT-ROP STUDY	361	70	14	5
ET-ROP STUDY	6,998	68	_	_

This table depicts the incidence of severe ROP among premature babies in the "CRYOROP study" and "ET-ROP study".

STUDIES	Patients	Prethreshold ROP (%)	Plus (%)	Zone I ROP (%)
CRYO-ROP STUDY	2,699	27	17	2
ETROP-ROP STUDY	2,320	37	24	9

DEFINITION OF ROP:

Retinopathy of Prematurity (ROP) is a disorder of retinal vasculature affecting t the developing or maturing retina of premature babies.

RETINAL VASCULOGENESIS:

Blood supply of retina constitutes:

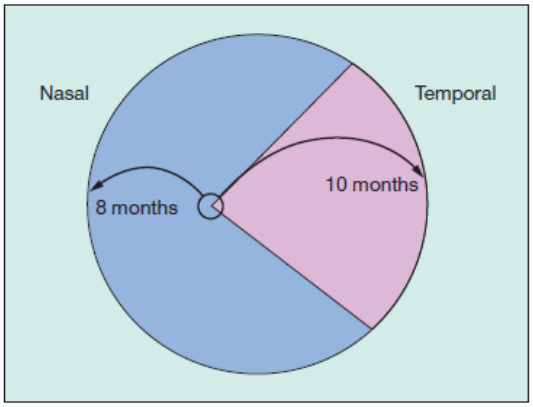
-Outer four layers of retina is supplied by choriocapillaries.

-Inner six layers of retina is supplied by central retinal artery.

Visual processing begins around 28 weeks of GA.

Visual responses can be measured from 32 weeks of GA.

Normally retinal vasculogenesis starts at optic disc around 16 weeks of gestation and it reaches the nasal oraserrata by 32 weeks of gestational age and temporal oroserrata by 40 weeks of gestational age.



Vessels reaches nasal ora serrata earlier than temporal because nasal ora serrata is at shorter distance from the optic disc when compared to the temporal side.

The Outer segment of photoreceptors becomes metabolically active by28 weeks of gestational age, so nutritional reqirement of the retina till then is less. During this time, the entire retina receive its blood supply from choroidal circulation by diffusion.The development of choroidal vasculature usually completes by 22 weeks of gestation.

At 28-32 weeks, when photoreceptor activates and vision begins, the metabolic demand of the retina increases and hence the need of blood supply also increases. But only little change occurs in the choroidal vasculature which does not meet the increased demand of the retina. Because of this, retina needs to meet its increased metabolic demands by its own vascular supply.

The two main laminar layers of the retinal vasculature constitutes the primary superficial layer and the ganglion cell layer in deeper retina. Network of fine capillaries interconnects the two layers. The maturation of the primary

vascular layer of the retina depends on the astrocytes development in the nerve fibre layer.

Astrocytes are glial cells which supports endothelial cells biochemically and also senses physiologic hypoxia and regulates VEGF.

One of the important factors in vasculogenesis is production of VEGF which creates a chemotactic gradient to promote retinal angiogenesis in the peripheral ora serrata.

From the optic nerve the astrocytic cells emerges and their migration progresses ahead of the maturing vasculature. Thus astrocytes can be seen in retina where retinal vasculature forms, and are well restricted to the inner layer of retina.

Astrocytes responds by expressing VEGF when there is a hypoxia state in the inner layers. It inturn induces the formation of the superficial layer of blood vessels.

Hyperoxia inhibits the formation of both normal and new blood vessel by down-regulating the expression of VEGF by astrocyte.

Insulin like growth factor(IGF-1) also plays vital role in retinal vascular development. IGF-1exerts its role by controlling the activation of VEGF. The availability of IGF-1 is highest at one month after birth and hence new vessel formation in ROP occurs at this time even though hypoxic insult occurs earlier.

ROP PATHOGENESIS:

ROP PHASES:

Phase 1: Phase of hyperoxia-vasocessation

The hyperoxic insult to the newborn can occur at any point from the birth to 30-32 weeks of post conceptional age. It may be even to the exposure of room air or fluctuations in oxygen supplements.

The infant's retina become hyperoxic (even in room air)

↓

decline in VEGF level

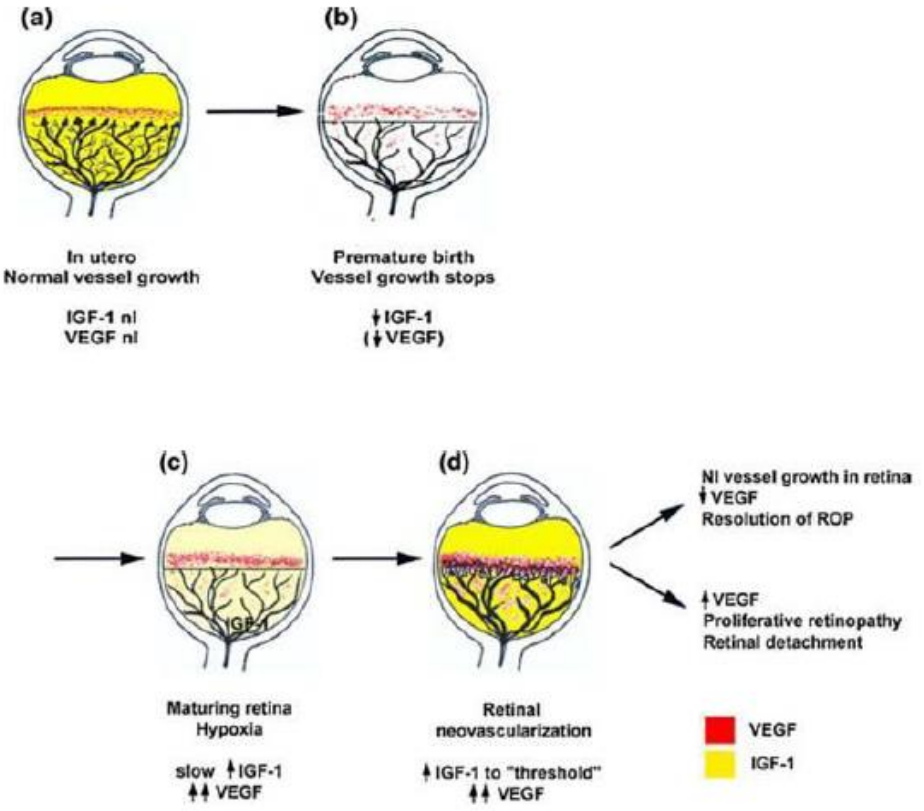
↓

vasculogenesis is stopped for a time at the junction of vascular and avascular retina

↓

Increased risk for ROP development.

Hyperoxia causes endothelial cell damage by various mechanisms such as free radical damage thereby arresting the vasculogenesis.



The production and the level of IGF-1, erythropoietin and other cytokines are influenced by premature birth. The environmental change also affects the normal physiological vascular growth of retina. As placenta and amniotic fluid of preterm babies provides very less amount of IGF-1 , the activation of VEGF production is reduced thus affecting the retinal vasculogenesis.

<u>Phase 2: relative hypoxia - revascularisation phase</u>:

•This phase occurs at 32-34 weeks of post conceptional age.

Before 32 weeks of gestation, the metabolic demand of retina is low as the photoreceptors are not yet fully functional. After 32 weeks,with the retinal

maturation there is an increase in metabolic demand and oxygen consumption leading to a state of relative retinal hypoxia.

• This inturn results in an increased or abnormal level of pro-angiogenic growth factors such as erythropoietin and VEGF.

Overtime, the levels of IGF-1 recover postnatally and when it reaches a critical threshold, VEGF induced angiogenesis is triggered leading to development of ROP i.e, disordered proliferative growth of vessels in the retina which later can extend into the vitreous causing further complications.

There were many multicentral trials conducted to analyse the risk factors responsible for ROP. Significant among them are CRYO-ROP, LIGHT-ROP,ET-ROP. They analysed the risk factors, progression , prognostic factors of the disease. It analysed Gestational age, Birth weight, Gender,Single or multiple birth and race. It also analysed the datas specific to retinal findings of ROP such as onset of disease, Zones or area of the disease involved, stage, progression , presence of plus disease.

Decreased Gestational age and low birth weight was correlated with incidence and severity of ROP.

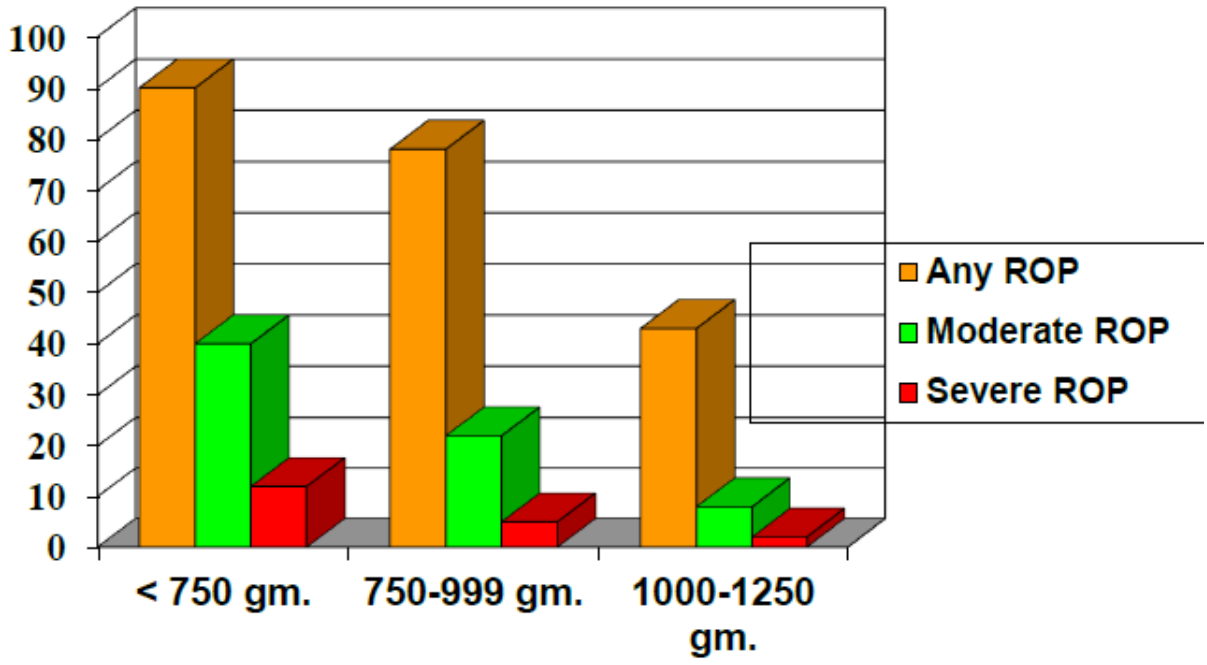
Race does not contributes to the severity or stage of ROP but it has effect on the incidence of ROP. Among the gender, both the sexes contribute equally. Multiple birth has higher risk compared to single birth.

In 1991, CRYO-ROP correlated the prethreshold ROP and threshold ROP onset with the Gestational age and Post menopausal age.

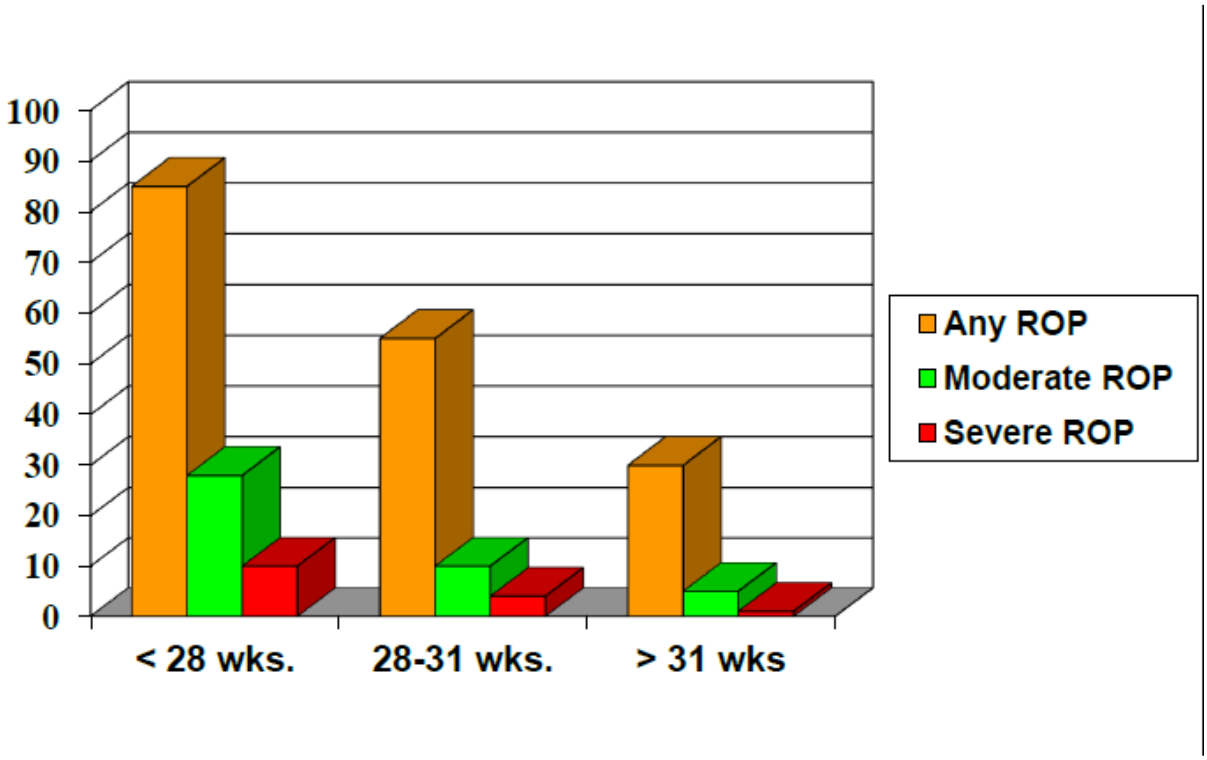
In CRYO-ROP, babies were divided by their birth weight such as 1,000–1,250 g, 750–1,000 g, and less than 750.It was noted that since the youngest and the most premature babies were more susceptible to face longer environmental exposure ,they develop severe ROP.

STUDIES	MEDIAN ONSET OF PRETHRESHOLD ROP (PMA)
CRYO-ROP study	36.1 weeks
ET-ROP study	36.1weeks

ROP INCIDENCE WITH BIRTH WEIGHT:



ROP INCIDENCE WITH GESTATIONAL AGE:



"CRYO-ROP" STUDY:

The major Prognostic factors:

-Status of ROP

-Zone which is involved

-Plus disease.

Minor prognostic factors:

Circumferential extension of stage 3 disease

Difficulty in assessing the progression of disease.

RISK FACTORS OF ROP:

The classical proven risk factors are low gestational age,low birth weight and fluctuation in oxygen supplementation. There are many other risk factors proposed to cause ROP.

OXYGEN:

The underlying pathogenesis of ROP with oxygen lies at the level of choroidal circulation where in the autoregulation for varying partial pressure oxygen fails. Hence in hyperoxic state, when retinal vasculature constricts, choroidal vessels will not constrict.As a result , there will be a shift of oxygen from choroid to retina further aggravating the constriction site.

Hyperoxia also affects the growth of spindle cell and its maturation thus impairing the retinal vasculogenesis. For babies who are under high risk for ROP due to oxygen exposure, state of chronic anaemia in their mothers is found to be a protective factor.

In oxygen supplementation,it is the fluctuation of oxygen level which is most important than the continuous delivery of oxygen. Currently modern day facilities in NICU monitors the saturation level of oxygen and deliver titrated level of oxygen thus reducing the risk of ROP.

GENETIC FACTORS:

The role of genetic factors as a risk to ROP was proposed in early 1990s by observing the variations among the ethnic groups.The variation in races noted pointed the role of genetic, diet, socioeconomic factors in the development of ROP.

Recent studies of genetic approach among monozygotic twins has proved strong correlation between genetic factor and ROP. The genes proven to be involved are " Norrin, Lrp 5, Frizzled 4".These genes are found to be involved in wnt signaling molecular pathway and they were found to be mutated in advanced ROP cases.

This probably explains why some babies progresses to advance stages despite timely intervention while some other babies do not progress.

Other risk factors for ROP proposed are

- blood transfusions,
- artificial ventilation for more than 7 days,
- poor postnatal weight gain
- hyperglycemia,
- Low IGF -1,
- surfactant therapy ,
- systemic infections,
- patent ductus arteriosus.
- bronchopulmonary dysplasia and
- intraventricular hemorrhage

HAEMOGLOBIN AND ROP:

Many studies conducted have proved that ROP is more associated with HbA than HbF. This is why because of the high affinity of oxygen towards HbA. In preterm babies because of high concentration of HbF, it serves as an

protective factor for ROP. As age increases, the concentration of HbF shifts towards HbA thus increasing the risk for developing ROP.

"ROP SCREENING AND PREDICTION":

Primary goal of ROP screening is to diagnose the babies at the earliest so that timely intervention can be given if ROP present thus preventing the blindness and other complications of advanced ROP.

"Treatment window of oppurtunity"- Detection of disease at a stage where effective treatment can be provided and avoidance of diagnosis at late stages where treatment would be ineffective.

The term "ROP screening" is misleading, usually screening in our health care system is done by non-physicians and lab technicians where as ROP screening is conducted professional ophthalmologist who has experience in it.

Screening the high risk babies aids in diagnosing and treating the ROP timely.

NATIONAL NEONATOLOGY FORUM(NNF)- SCREENING PROTOCOL:

-Babies born <34 weeks of gestation or/and

-Babies born with birth weight <1750 grams,

-Babies born between 34-36 weeks and birth weight 1750-2000grams should be screened if they have other risk factors for ROP such as Respiratory distress syndrome , prolonged oxygen exposure ,cardiorespiratory support, chronic lung disease,, fetal haemorrhage, sepsis, apnoea, blood transfusion, , intraventricular haemorrhage).

-Baby born >28 weeks of gestation ROP screening should be conducted at 4 weeks after birth.

-Baby born <28 weeks of gestation or with birth weight <1200grams should be screened at 3 weeks after birth.

By the current protocols, among the babies screened for ROP 8% needs treatment. This emphasis the need for alternative regime which would be technically easier and implementable to assess and identify the high risk babies.

ROP CLASSIFICATION:

"INTERNATIONAL CLASSIFICATION FOR RETINOPATHY OF PREMATURITY(ICROP)":

ICROP guidelines were updated in 2005 which uses following terminologies:

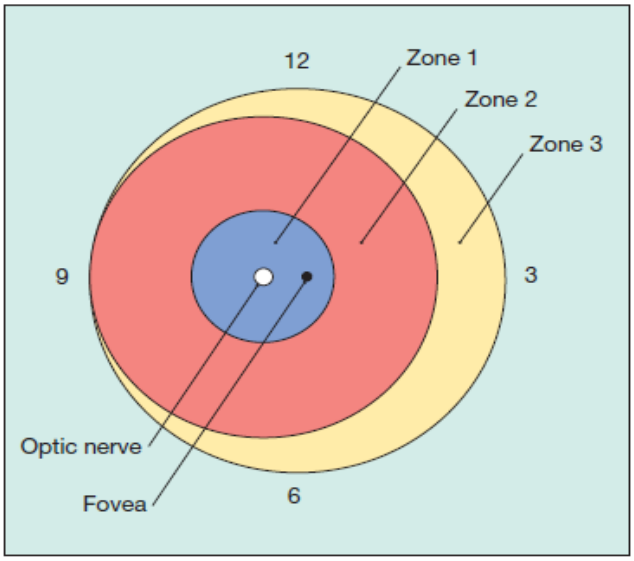
Zones - Describes the area of retina which is involved in ROP

Stage -Describes the severity of the disease

Clock hours -Describes the extent of the disease(no longer used)

Plus disease - Characterised by dilated and tortuous retinal vessels in any zone associated with or without engorgement of iris, rigid pupil and hazy vitreous.

ZONES OF RETINOPATHY OF PREMATURITY:



ZONES:

ZONE I: Circle with radius double the centre from the centre of the optic disc to the centre of the fovea.It subtends around 60 degree of arc.

Zone I can be clinically assessed using +28D lens by placing the nasal margin of the optic nerve head in the field of view of the lens with zone I being the temporal limit .

ZONE II: Concentric circular area with the nasal border at the nasal oraserrata and the temporal border almost at the anatomical equator of the retina.

ZONE III: Remaining area of retinal crescent temporal to zone II. Zone III vascularises at the last.

STAGES:

There are 5 stages as follows

STAGE1: Line of demarcation

STAGE2: Ridge of elevated tissue.(intraretinal neovascularisation)

STAGE3:Extraretinal neovascularisation.

STAGE4: Partial retinal detachment

4a-Macular spared

4b-Macular involved

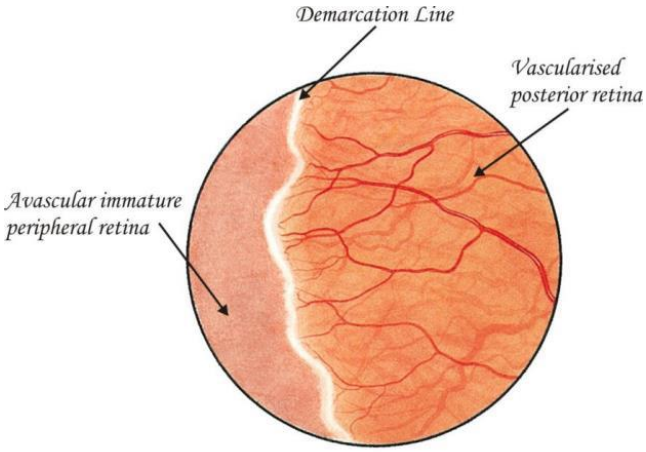
STAGE5-Total retinal detachment

STAGE 1 – "DEMARCATION LINE":

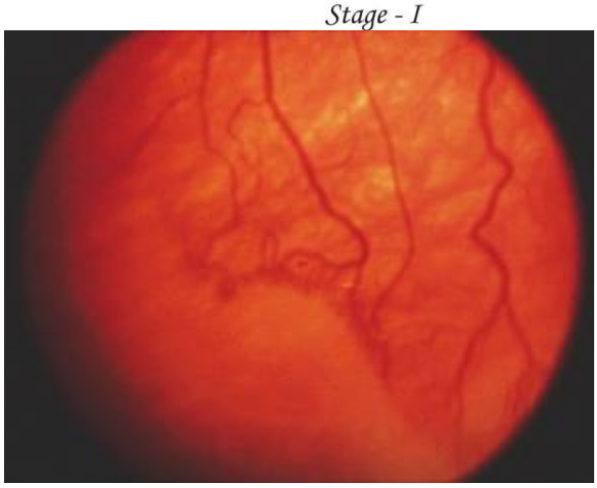
- Clinically first sign of ROP to occur.
- Appears as a flat whitish structure between vascular and avascular retina.
- Present within the plane of retina.
- It may be due to abnormal vessels arcading .
- It either regress or progress to stage 2 ROP.
- By Garner, anatomically demarcation line has two distinct zones-

"vanguard", the anterior zone of spindle-shaped cell mass which is considered as progenitors of the differentiated vascular endothelium.

These cells when undergo hyperplasia the demarcation line becomes visible ophthalmoscopically.



Stage - I



STAGE 2– "RIDGE"

- The stage 1 demarcation line progresses to ridge by expanding the width and height and it extends centripetally within the globe.

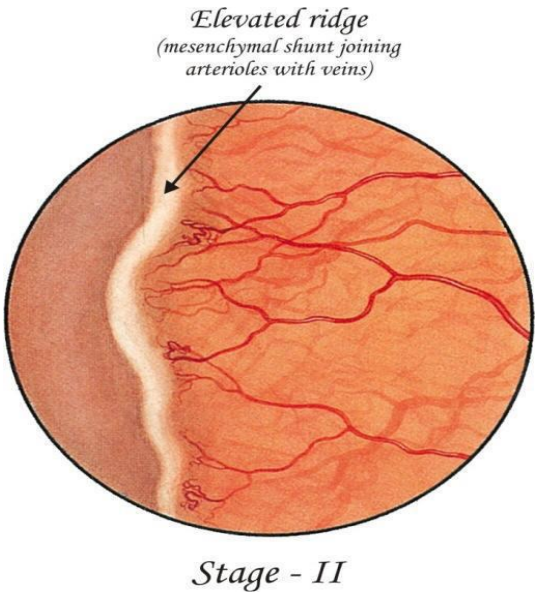
- Colour of the ridge is usually white or pink

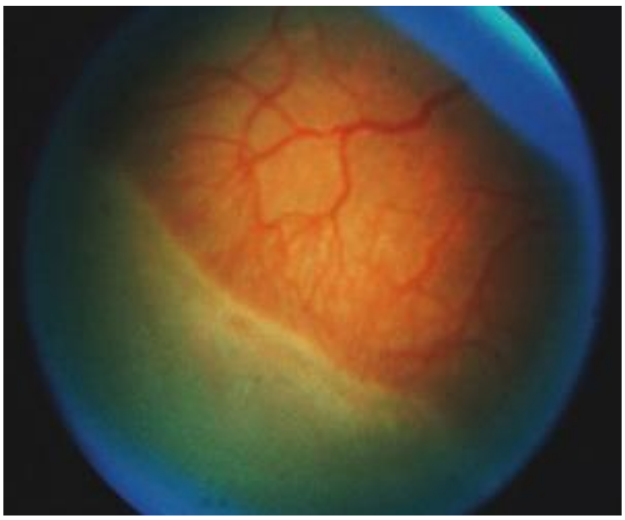
- In rare cases vessels leave the retinal plane to enter the ridge.

- Posterior to the ridge, "popcorn"vessels- small tufts of new vessels may be seen.These vessels are not attached with the ridge.

- Garner explain ridge and popcorn vessels as a endothelial cell proliferation and its organization into vascular channels."

These channels shows leakage on Fundus fluorescein angiography.





STAGE 3 – "RIDGE WITH EXTRARETINAL FIBROVASCULAR PROLIFERATION":

- In this stage,fibrovascular proliferation extends from the ridge towards vitreous extraretinally..

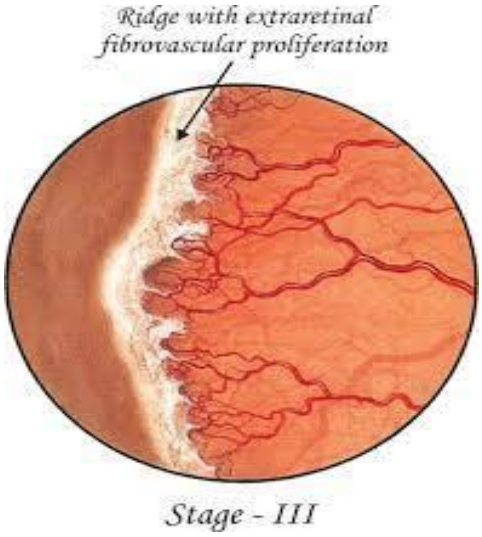
- Proliferation is localized and is continuous with the posterior aspect of ridge, which appears as a ragged border.

-Based on the proliferation this stage can be subdivided into three stages namely mild, moderate and severe.

-By Foos, histopathological appearance of extraretinal vascularisation can be

‘placoid’, or ‘polypoid’, or ‘pedunculated’.

-Among these, the most common and important type is placoid, as this pattern can lead to detachment of the retina.



STAGE 4 –PARTIAL RETINAL DETACHMENT:

STAGE 4A: “EXTRAFOVEAL RETINAL DETACHMENT”

- This stage involves tractional detachment at the site of extraretinal fibrovascular proliferation due to vitreous traction .Retinal detachment is concave. This stage involves peripheral part of the retina without involving macula.

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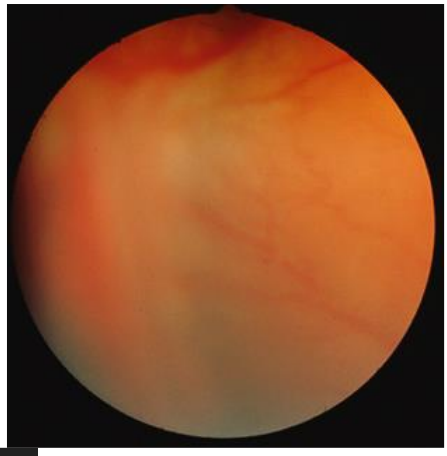
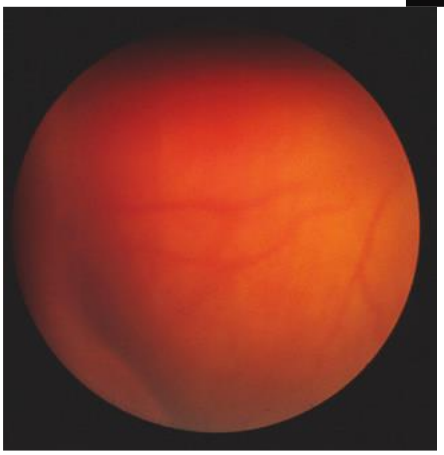
- Retinal detachment may be segmental or may be circumferential for 360 degree. If there is no posterior extension prognosis will be relatively good. Reattachment may occur spontaneously with no affect to function of the macula.

BOTH EXUDATIVE AND TRACTIONAL

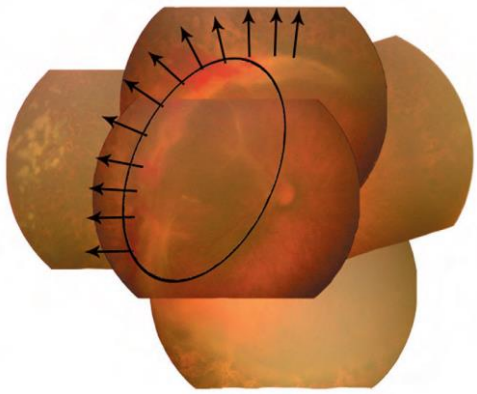




EXUDATIVE

STAGE 4B: "PARTIAL RETINAL DETACHMENT INVOLVING THE FOVEA"

This stage includes partial retinal detachment involving the macula as a result of fibrovascular proliferation. Because of macular involvement visual prognosis is poor.



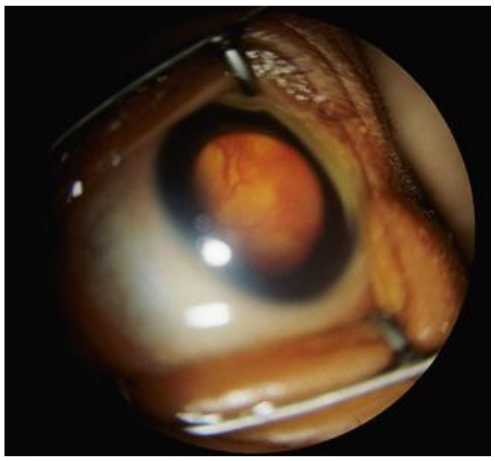
STAGE 5: “TOTAL RETINAL DETACHMENT”

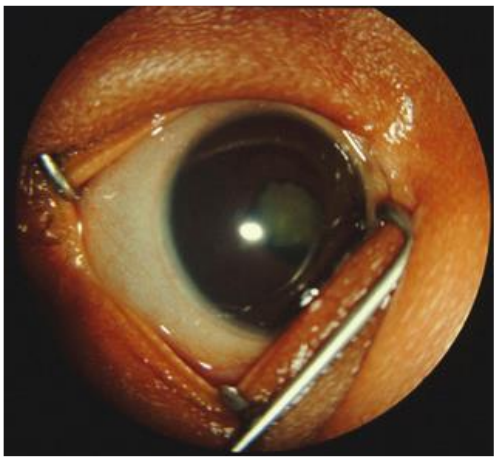
In this stage retinal detachment is funnel-shaped and based on the funnel shape it can be classified as “open” or “closed” and anteriorly or posteriorly .

- The first common type is concave shape and it is open both anteriorly and posteriorly. It extends upto the disc.
- Second type is funnel shaped which is narrow both anteriorly and posteriorly.
- Third type is funnel shaped which opens anteriorly and narrows posteriorly.
- Fourth least type is also funnel shaped which narrows anteriorly but open posteriorly.

These types are diagnosed ultrasonographically.

OPEN FUNNEL RD	CLOSED FUNNEL RD



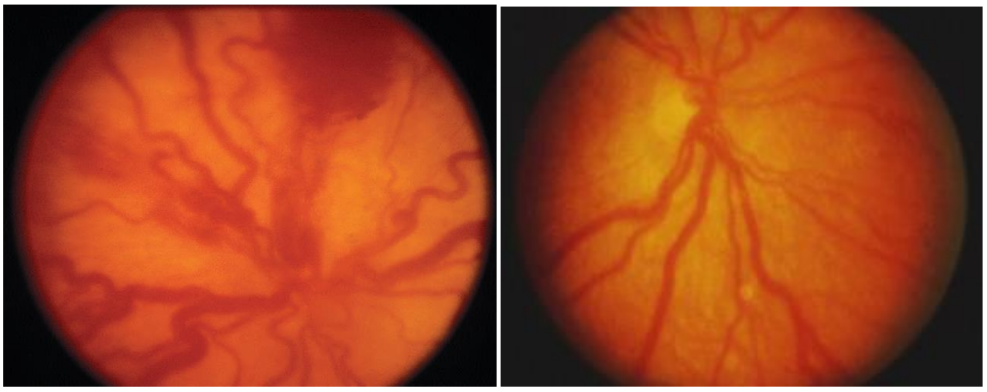


“PLUS” DISEASE:

Characterised by dilated and tortuos retinal arteries and veins in any zone.

- It is associated with rigid pupil, engorgement of iris and hazy vitreous.
- Indicates poor prognosis.
- It is postulated that plus disease may occur either as blood shunts from the ridge or as the blood vessels itself produces increased VEGF.

PLUS DISEASE



“PRE PLUS” DISEASE:

By Revised ICROP , “preplus disease” is defined as “dilatation and tortuosity of vessels in the posterior pole that is insufficient to meet the diagnosis of plus disease”.

“AGGRESSIVE POSTERIOR” ROP(AP-ROP):

-Used to describe disease of posterior zone (zone I or posterior zone II)

- Presence of plus disease which would be dispropotionate to the extent of retinopathy.

- This stage can progress to detachment of the retina directly without the evolution through classic stages.

- It can possess flat neovascularisation and also circumferential vessels can be seen at the junction between vascularised and avascularised retina.

RETINAL FINDINGS OF "REGRESSED ROP":

Residual changes in regressed ROP is classified based on the location as,

- Retinal peripheral changes and
- Posterior retinal changes

These peripheral and posterior retinal changes are further subdivided into retinal and changes.

Peripheral vascular changes:

- Circumferential interconnection of vascular arcades.
- Failure of peripheral retinal vascularisation.
- Telangiectatic vessels
- Retinal vessels exhibit abnormal non-dichotomous branching.

Peripheral retinal changes:

- Lattice-like degeneration , retinal breaks

- Pigmentary changes

- Rhegmatogenous or tractional retinal detachment.

Posterior Vascular changes:

- Abnormality seen at the angle of insertion of the major temporal arcade

- Vascular tortuosity

- Straightening of blood vessels in temporal arcade

Posterior Retinal changes:

- Retinal draaging over the disc

- Pigmentary changes

- Ectopia and distortion of the macula.

OCULAR FINDINGS OF "REGRESSED ROP":

- ✓ Astigmatism
- ✓ High myopia
- ✓ Anisometropia in unilateral ROP. It can be seen in bilateral ROP also.
- ✓ Strabismus may develop as a consequence of poor vision(sensory

deprivation)

- ✓ Amblyopia of the diseased eye
- ✓ Nystagmus
- ✓ Cataract due to fibrovascular proliferation extending till the anterior vitreous phase.
- ✓ Glaucoma
- ✓ Corneal changes such as band shaped keratopathy, acute hydrops and corneal curvature irregularities .

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CICATRICIAL DISEASE:

Cicatricial complications occurs in 20% of infants with active ROP. It ranges from mild to extremely severe form. More advanced disease and more posterior location at the time of involution may endup with worst cicatricial sequelae.

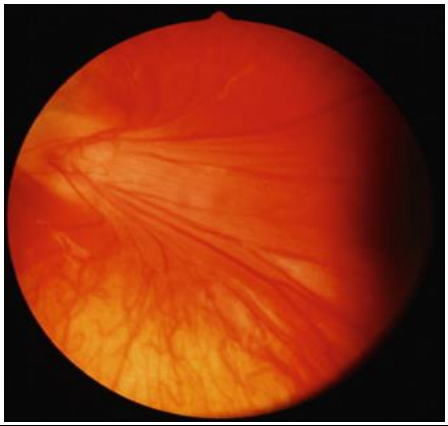
Stage 1: Pigmentary changes in retinal periphery and hazy vitreous base .

Stage 2: Temporal vascular arcades straightens as a result of vitreoretinal fibrosis. It drags macula and the optic nerve head.

Stage 3: Severe fibrosis extends to peripheral retina along with contracture resulting in falciform retinalfold.

Stage 4: Retrolental fibroplasias ,incomplete ring of a retrolental fibrovascular tissue alond with total RD occurs.It results in progressive shallowing of

the anterior chamber due to forward movement of the iris-lens diaphragm. Subsequently anterior synechiae and secondary angle closure glaucoma develops.

MACULAR HETEROTOPIA	MACULAR FOLD
	

Cicatricial macular changes classification: "MS – Macular score"

"MS-0 Normal

MS-1 Macular ectopia

MS-2 Macular fold

MS-3 Macular detachment

MS-4 Total detachment"

FOLLOW UP PROTOCOL BASED ON RETINAL FINDINGS:

("Zone I:

Immature retinal vascularisation – 1-2 weeks follow up

Stage 1 or 2 – 1 week or less follow up

Regressing ROP – 1-2 weeks follow up

Zone II:

Immature retinal vascularisation – 2-3 weeks follow up

Stage 1 – 2 weeks follow up

Stage 2 – 1-2 weeks follow up

Stage 3 – 1 week or less follow up

Regressing ROP – 1-2 weeks follow up

Zone III:

Stage 1 or 2 – 2-3 weeks follow up

Regressing ROP – 1-2 weeks follow up")

The followup schedule must be done regularly and the recordings should be documented.

"ET-ROP treatment guidlines includes,

Type 1 ROP:

It is a new threshold or severe ROP. Treatment for Type 1 ROP is peripheral retinal laser ablation. It includes

Stage 2 or 3 with plus disease involving zone II

Stage 1, 2, or 3 with plus disease involving Zone I

Stage 3 without plus disease involves Zone I

Type 2 ROP:

It refers to low risk prethreshold ROP or mild ROP. Treatment for type2 ROP is to observe the case for progression.It includes

Stage 3 without plus disease involving Zone II

Stage 1 or 2 without plus disease involving Zone I".

Agressive posterior ROP(AP-ROP) needs ablative laser photocoagulation therapy. Stage 4 (Partial RD) or stage 5 ROP(Total RD) requires surgical intervention.

DISCONTINUATION OF SCREENING:

ROP screening or follow up schedule can be stopped, unless the eyes recieved treatment in the form of either laser or anti-VEGF for severe ROP, if any one or more of the following criteria are present.

- Complete vascularisation of retina.
- Retinal vascularisation of zone III with no previous zone I ROP or zone II ROP
- Zone III regressing ROP with no abnormal vascular tissue capable to reactivate in zone II or zone III.

Decision must be individualised based on the course of the disease.

DIFFERENTIAL DIAGNOSIS:

1. Retinoblastoma

- One of the differential diagnosis for stage 5 ROP.

  Differentiang feature is the history of prematurity and asymmetrical presentation. Diagnosis is confirmed by the ultrasonography.

- USG in retinoblastoma shows posterior mass lesion with calcification whereas in ROP multiple echoeic pattern behind the lens or the retinal detachment is seen.

2. Familial Exudative vitreoretinopathy:

- Clinically indistinguishable from acute ROP, resembles stage 1 to 3 ROP.
- It can be differentiated from ROP by no history of prematurity, family history, asymmetry between both the eyes. Familial exudative retinopathy may present anytime from the birth till first decade.

3. Coat's disease:

- This disease is due to abnormal telangiectatic retinal vessels. Features are retinal edema as a result of profuse leakage from the telangiectatic vessel, yellowish green subretinal fluid and finally exudative detachment.

Initial presentation of these cases is leucocoria.

4. **Persistent hyperplastic primary vitreous (PHPV):**

- Congenital anomaly seen in term infants. Mostly unilateral.

  It may be associated with microcornea. Greyish white membrane is seen behind the lens mimicking ROP sequeale.

- In ROP vessels can be seen behind the lens in the fibrovascular component and posteriorly retinal detachmentis seen. In PHPV, no retinal detachment is present ,a stalk extends from the optic disc to posterior of the lens surface.

5. **Incontinentia pigmenti:**

- It is a multisystem disorder affecting females. It affects skin, tooth and nervous system.
- Ocular features shows preretinal neovascularisation, non perfusion of peripheral retina, vitreous haemorrhage and finally tractional retinal detachment. Term born with characteristic vesiculobullous lesion excludes ROP.

6. **Norrie's disease:**

- X-linked disorder has features of leucocoria, deafness and mental retardation. Presents with leucocoria at 4-6 weeks of age.
- In ROP leucocoria presents at very late stage i.e., stage 5 ROP.

PREVENTION:

Primary prevention of ROP is to be targeted in decreasing the incidence of preterm birth and low birth weight babies.

- Better monitored prenatal care, avoidance of illegal drug would help in promoting healthy gestation and thus reducing ROP incidence.
- The "STOP-ROP study" a multicentred trial

conducted in 1990s aimed at eliminating the hypoxic states which promotes the formation of new vessels.

- This trial was conducted on 694 infants suffered from prethreshold ROP. Babies were randomly assigned in two groups. One group maintains Oxygen supplementation saturation levels at 96%-99% .Another group at 89%-94% which is a conventional saturation level.
- There was no statistical difference found between the two groups (41% versus 48%) in the progression of threshold ROP .In the subgroup of babies with prethreshold ROP with no evidence of plus disease, a post hoc analysis was done .The result showed a significant reduction

(32% versus 46%) in progression to threshold ROP among the supplemental arm.

- Many studies conducted from 2003 to 2006 on maintainence of oxygen saturation level between 85%-93% showed a significant decrease in prethreshold ROP and "severe ROP".

- There are some other studies with increased mortality of the babies if oxygen saturation level was maintained between 85%-89%" even though it is associated with reduced incidence of severe ROP.

LIGHT –ROP TRIAL:

- LIGHT–ROP trial analysed the hypothesis that when

extrauterine exposure to light is reduced by wearing light–blocking goggles from the birth to 31 weeks of postmenstural age would reduce the incidence of ROP.But it was found to have no statistical difference between the control and treatment groups.

- Recent experiments have suggested that exposure to gross light in high quantity during the late gestation may result in hyaloidal regression and can affect the development of the retinal vessels.
- Certain studies was conducted to test the effect of antioxidants such as vitamin E and Dpenicillamines in reducing ROP incidence .The results were controversial to each other.

RET CAM II:

Ret cam II is the screening method used to detect retinopathy of prematurity. As the number premature babies is increasing due to its increased survival rates, Retcam helps to screen the premature infants with ease . Images of Ret cam are clear and also reliable.

Portability of Ret cam made it a easy tool for diagnosis and teaching purpose. Ret cam II is actually a contact retinal camera which has to be placed over the cornea by using the coupling fluid. Wide field images can be captured and converted into high resolution digital colour photograph.

TREATMENT:

- ROP treatment aims at the maximal preservation of neurosensory retina both structurally and functionally with minimal complications. Clinical studies conducted showed that peripheral diode laser photocoagulation is nuch superior to cryotherapy in treating ROP.
- Earlier cryotherapy was used in treating ROP since 1972. The CRYO–ROP study was conducted among 291 infants who had "threshold ROP" and the babies were randomized to either cryotherapy within 72 hours of diagnosis or observation.
- The 10-years CRYO-ROP study showed that among the untreated eyes of threshold disease involving zone II , 62% had a poor visual outcome. Whereas among untreated threshold ROP of zone I, 87% had poor visual outcome.
- As there was a significant decrease in unfavourable complications such as retrolental tissue, posterior retinal folds, retinal detachment among the treatment group (i.e.,31% treated versus 51% observed), the "CRYO-ROP study" was stopped earlier at that time. But 254 preterm babies

whom were followed for fifteen-years even after the study period showed the long-term treatment benefits.

- The study group showed reduced incidence of poor visual acuity among the treated eyes. (i.e., 64% observed versus 45% treated).
- Indirect laser photocoagulation was not widely on market during the CRYO-ROP study period.
- There are certain studies suggesting that laser treated eyes showed better structural and functional outcomes than cryotherapy treated eyes.
- Later in times, a study “Early Treatment of Retinopathy of Prematurity(ETROP)” was conducted to determine the effect of early treatment in visual outcome.

In ETROP study, “prethreshold ROP” was further subdivided into type1 ROP and type2 ROP. In type1 ROP there was more than 15% chance of getting unfavourable outcomes based on the characteristics of the eyes and infant from the CRYO-ROP.In type 2 ROP, inthere was less than 15% chance of getting unfavourable outcome.

ETROP study suggested that type 1 ROP is beneficial from peripheral laser photocoagulation ablative treatment and type 2 ROP can be followed up twice weekly till the disease shows no progression to higher-risk category or shows improvement .

By the end of 9 months, results showed that the group received treatment at prethreshold ROP had reduced unfavourable visual outcomes of about 14.5% whereas it was 19.5% in the conventional group i.e., treatment for threshold disease.These results showed statistically significant difference.

When the babies of early treated eye were followed at the end of the 6 years only few of them had unfavourable structural Outcomes . But visual acuity was not affected significant at 6 years. Even a subgroup analysis showed improved visual acuity for those who received early treatment for ROP involving zone I.

BEAT – ROP STUDY:

"BEAT-ROP" used bevacizumab (anti-VEGF antibody), intravitreally at a dose of 0.625 mg in 0.025 ml in 150 infants.It was beneficial in babies who had zone I stage 3+ ROP. Bevacizumab acts against the vasculogenesis factor and eliminates the chance for abnormal angiogenesis.

The sample size of this study was not sufficient to assess the effects of the drug on the developing brain and adverse effects.It also did not address dosage of the drug. Also bevacizumab is not yet FDA approved drug for treating ROP.

Bevacizumab was used in this study only for zone I stage 3+ROP.Detailed informed consent were obtained. Follow up were done weekly after the treatment until the retina vascularises completely. Follow up period should be longer than for the conventional laser ablation as recurrent stage 3 ROP is more common with anti-VEGF than the laser ablation treatment. Follow up should

be assured after bevacizumab treatment especially after the discharge or transfer of the baby from neonatal unit.

CURRENT RECOMMENDED GUIDELINES FOR TREATMENT:

- According to ETROP, type 1 ROP should receive laser ablation of avascular retina within 72 hours of its detection.

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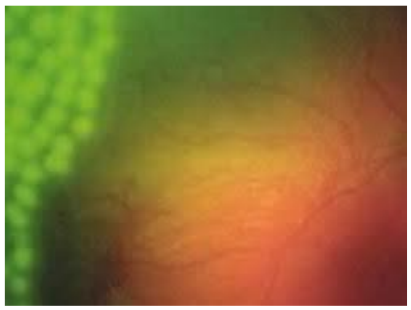
- Laser photocoagulation burns should be placed from the ora serrata upto the avascular retina anterior to the ridge for 360 degree. Burns should be grey to grey white with one-half laser burn width space between them.
- Rarely ocular complications can occur such as mispositioned laser burns, cataract, post laser inflammation, to the anterior rotation of lens-iris diaphragm leading to glaucoma secondary, vitreous hemorrhage, and pthisis bulbi very rarely.
- Systemically, infants may develop apnoea, bradycardia and cardiopulmonary arrest during or following the procedure and so the babies should be followed up closely for the same.
- Topically steroids and cycloplegics are applied for a short time after the procedure. First follow up should be within 3-7 days and then it can be weekly or more frequently.
- Persistent disease or recurrence is treated with additional laser ablation and vitreoretinal surgery must be considered for progressive stage 4 ROP.

“LASER PHOTOCOAGULATION”:

The basic principle on ablating the ischemic avascular retina is that it stops the release of angiogenic factors.



Advantages:

- As cryotherapy is limited to anteriorly located lesions, laser photocoagulation can be used for treating more posteriorly located lesion,
- It promises good structural and functional outcome,
- General anaesthesia is not required.

Procedure:

- Obtain informed written consent from parents or legal guardian before starting the procedure.
- Nature of the disease, chances of its progression, its complication, long term sequelae, advantage and disadvantage of the treatment should be explained to the parents.

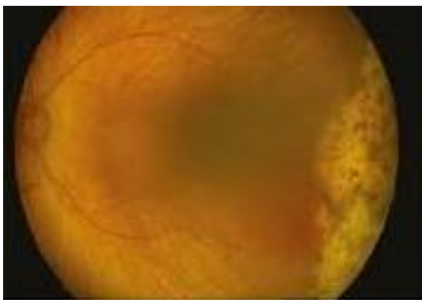
❖ Chances of retreatment, surgical intervention, success rate and the importance of long term follow up to be explained.

- Oral feeds to be stopped at least half an hour prior to the procedure.
- Presence of neonatologists and anaesthetist during the procedure should be ensured.
- Dilate the pupil adequately.
- If the baby is in incubator , procedure to be done in incubator itself with sloping walls.
- Portable frequency doubled Nd: YAG laser or infra-red diode laser(most commonly used), or an argon laser can be used.
- Laser is delivered by indirect ophthalmoscope. As diode laser penetrates the eyes even with tunica vasculosa lentis and vitreous haemorrhage, it is used worldwide than the other lasers for ROP.
- Antibioyic eye drop is applied to the eye to be treated. Paediatric lid speculum is applied. Indentation can be done with wire vectis or scleral depressor.
- + 20 or +28 D aspheric lens can be used for the visualisation of the retina.
- Power of diode laser can be delivered within the range of 300 to 400mw and the duration of laser can be 300 to 400ms.
- Laser settings should be set at the minimum to produce light grey burns.
- Avascular retina is ablated from the ridge to the ora serrata as near confluent burns with one half burn width apart.
- Confluent treatment showed less progression than the dense laser

treatment.

- ❖ In cases of aggressive ROP, laser spots are delivered to the areas enclosed by flat neovascular loops .
- ❖ Pupils can be dilated mechanically if they are rigid or not dilating due to tunica vasculosa lentis.
- ❖ Frequent instillation of carboxymethyl cellulose topically during the procedure provides the clear visualisation of the retina .
- ❖ Topically antibiotic -steroid eye drops to be applied for one week following the procedure to control the inflammation.
- ❖ Some premature infants may develop apnoea during the laser treatment and they immediately need resuscitation and ventilator support.

BEFORE THE LASER TREATMENT



AFTER THE LASER TREATMENT

· Conjunctival congestion, mild chemosis and subconjunctival haemorrhage may occur in some cases of excess scleral indentation.

· Rarely preretinal and vitreous haemorrhage can occur

- Intensive photocoagulation sometime can lead to anterior segment ischemia and also necrosis.

FOLLOW UP:

Follow up should be done after 1week from the procedure.

During the follow up things to be assessed are

- Extent of the plus disease
- Any presence of skip areas
- The status of the ridge and also fibrovascular proliferation if any
- Vitreous organization
- Tunica vasculosa lentis
- The Presence or absence of vitreous haemorrhage

In the of presence of significant plus disease with skip areas during the follow up additional laser can be considered. If Plus disease is seen without skip areas, frequent weekly follow up must be done. Follow up should be continued till the ROP regresses.

If no fibrovascular proliferation is seen, follow up is done till 6 months of age. Whereas in the presence of significant fibrovascular proliferation follow up should be at weekly interval to check for the tractional detachement of the retina .

SURGICAL MANAGEMENT FOR RETINAL DETACHMENT:

· ETROP study says that 16% of study group with type 1 ROP progresses to retinal detachment in at least one of the eyes.

· Retinal detachment can be classified as

- Rhegmatogenous
- Effusive (serous),
- Tractional(fibrovascular)

· Serous RD in stage 4 ROP often resolves spontaneously. Treatment plan either observation or surgical intervention is individualised. Retinal detachment can also occur within 12 weeks of laser treatment. In ETROP study,14% of eyes developed RD received laser treatment.

· Treatment for progressing stage 4 ROP is the lens-sparing vitrectomy. It releases fibrovascular traction and thus preventing the progression to stage 5 ROP and hence macular structure can be preserved.

· In certain cases, sclera buckling procedure can also be considered for the progressing stage 4 ROP.

· Treatment modalities for stage 5 ROP includes either only scleral buckle or vitrectomy with or without scleral buckle.

Despite of the interventions poor outcomes are seen in the presence of vitreous haze, plus disease and persistent neovascularisation. Scleral buckling has its own disadvantages such as high myopia leading to anisometropia and amblyopia.

OTHERS THERAPIES:

Other treatment modalities are

- Anti VEGF,
- IGF -1,
- Stem cell therapy,
- Omega 3 poly unsaturated fatty acid,
- Modulators of metabolite signaling growth factors.

VISUAL REHABILITATION:

❖ As a sequale of ROP infants are more likely to end up with high myopia, squint, amblyopia, heterotropia of macula and glaucoma.

❖ Aphakic infants or those who underwent scleral buckling requires special rehabilitation for the consequent high refractive error.

❖ ROP for whom macular vision is affected spectacles should be given to improve the vision and also it act as a protecting agent against ocular trauma.

❖ ROP infants can have poor vision due to other comorbidities such as

hydrocephalus,intraventricular hemorrhage and cerebral visual impairment.

MEDICOLEGAL CONSIDERATIONS:

Screening the premature infants for early diagnosis of ROP and timely treatment has major role in practicing of ophthalmology. There are mainly three things to be aware in ROP care which putforth both the premature baby and the whole health care team at risk.

Firstly, ROP risk premature babies typically would have multiple medical consultations for their care. Hence treating ophthalmologists should be aware of the status and the demographical location of the babies they follow such that screening schedules are not missed.

Secondly, parents of preterm infants are usually overwhelmed and so it is very essential to ensure their compliance for screening, regular follow up and for the treatment.

Thirdly, window for treating the ROP is very short and it may require transferring the critical patient. The whole team of Ophthalmologists, Neonatologists and nurses would be under the litigation when ROP protocols was broken.

Ophthalmologists who is examining and treating the infant for ROP can minimize their exposure to lawsuits by well educating the parents and preserving the documentation of the medical record.

REVIEW OF LITERATURE:

1. "**Neonatal Bacteremia and Retinopathy of Prematurity**

The ELGAN Study

Kristi Washburn Tolsma, MD; Elizabeth N. Allred, MS; Minghua L. Chen, MD, MPH; Jay Duker, MD; Alan Leviton, MD; Olaf Dammann, MD, MS"

ELGAN STUDY was conducted in Germany among 1059 infants born before 28 weeks of gestation i,e. Extreme low birth weight babies. This study evaluated the association of early or late and presumed (treated with antibiotics for atleast 72 hours with negative blood culture) or definite (culture proven) neonatal bacteremia with an increased risk of severe retinopathy of prematurity (ROP).In this study reports showed that presumed early bacteremia was assosciated with plus disease (odds ratio [OR], 1.7; 95% CI,1.1-2.7)and definite early bacteremia with stage 3 to 5 disease (1.9; 1.1-3.2). In univariable analysis, presumed or definite late bacteremia showed increased risk for all 4 indicators of severe ROP. In multivariable analysis, presumed late bacteremia had increased risk for prethreshold or threshold ROP (OR, 1.8;95%CI,1.02-3.2). Definite late bacteremia had increased risk for prethreshold or threshold ROP (1.8; 1.1-2.9) and plus disease (1.8; 1.05-2.9). This study concluded that definite late neonatal bacteremia as an independent risk factor for both prethreshold or threshold ROP and plus disease.

2."Association of infection, blood transfusion and other clinical factors with retinopathy of prematurity (ROP)

S Akter1, R Parvin2, B H N Yasmeen3, K S Anwar4, M M Hossain5"

This prospective observational study was conducted at special care baby unit (SCABU) and Intensive care unit of Dhaka Shishu Hospital in Bangladesh from July, 2006 to March, 2008 to assess the risk factors of ROP among premature (34 weeks) and/or VLBW (1500 gm) neonates. Neonates were followed daily for any significant risk factorsto record certain clinical factors . Infants were divided into two groups "No ROP group"(n=35), and "ROP group" (n=23). Comparative analysis of risk factors was done between the two groups. The study evaluated the significance of risk factors such as VLBW, culture proven septicaemia, mechanical ventilation, mean total hours of oxygen inhalation, cumulative volume of blood transfusion, and also intra ventricular hemorrhage with ROP. Study concluded incidence of ROP study is 40% and VLBW, culture proven septicaemia (p=.005; CI, 2.50 to 9.99) and large volume of blood transfusion(p=.013; OR,.43; CI, .028 to .653 are significant risk factors.

"3.Fungal and bacterial sepsis and threshold ROP in preterm very low birth weight neonates.

Manzoni P[1], Maestri A, Leonessa M, Mostert M, Farina D, Gomirato G".

This study assess the incidence and severity of ROP between fungal or bacterial sepsis .This was a retrospective cohort study conducted on all neonates with birth weight less than 1500 g admitted in Italian third Level Neonatal Intensive Care Unit from 1997-2001. They used univariate analysis and multiple logistic regression to assess significant associations of all grades and threshold ROP in neonates with birth weight<1000 g, extremely low birth weight and 1000-1500 g. At multivariate analysis, only gestational age (P=0.03) and colonization by Candida non-albicans spp (P=0.03), fungal sepsis

(P=0.03) were found to be independent predictors of threshold ROP in ELBW neonates. The study concluded that it is fungal sepsis not bacterial significantly and independently associated with threshold ROP in ELBW neonates .

4.” **Incidence and Risk Factors of Retinopathy of Prematurity (ROP) in Neonates of Weight 1.5 to 2 kg**

Dr SPS Dhillon, Dr Ashwani Kumar , Dr Astha Rani, Dr Prempal Kaur , Dr MS Pannu “

This study was conducted in NICU, Government Medical College, Amritsar from August 2014 to July 2015 to find incidence and risk factors of ROP in neonates of birth weight 1.5-2 kg.70 children were screened for ROP of which 12 of them were diagnosed to have retinopathy of prematurity. Incidence of ROP was 17.1%. Stage 1 ROP, stage 2 ROP with plus disease were detected. In univariate analysis, oxygen supplementation for more than 7 days and sepsis were found to be significantly associated with ROP. The study concluded that infants with birth weight less than 2 kg with the risk factor of sepsis or oxygen supplementation for more than 7 days should be screened for ROP as they are more prone to develop ROP including the threshold ROP.

PART TWO

AIM AND OBJECTIVES:

1. To determine the association between septicaemia and retinopathy of prematurity among preterm babies.
2. To analyse septicemia as a risk factor for “severe ROP”.

STUDY DESIGN:

- Prospective observational study

STUDY CENTRE:

• Department of Ophthalmology, Government Rajaji Hospital, Madurai.

• Neonatal intensive care unit, Institute of Paediatrics, Government Rajaji Hospital, Madurai.

STUDY PERIOD:

• This study was conducted for a period 6 months from March 2018 to August 2018.

SAMPLE SIZE:

• Total of 100 babies included in the study.

ETHICAL APPROVAL:

• Institutional ethical clearance was obtained from the ethical committee, Government Rajaji Hospital, Madurai.

INFORMED CONSENT:

• Informed Consent for the study is obtained in written statement from parents or guardian of all the babies before enrolment for the study.

SELECTION OF STUDY SUBJECTS:

100 babies fulfilling the eligibility criteria referred from Neonatology Intensive Care Unit, GRH, Madurai whom were treated for culture proven late onset septicaemia with positive sepsis screen.

INCLUSION CRITERIA:

- Premature neonates of <34 weeks of gestation, of either sex, both inborn and outborn,
- Babies with birth weight <1.75 kg,
- Babies who satisfied Systemic Inflammatory Response Syndrome (SIRS criteria) and were treated for culture proven late onset septicaemia with positive sepsis screen.

EXCLUSION CRITERIA:

- Babies with features of clinical sepsis by SIRS criteria with negative blood culture report.
- Babies with early onset sepsis
- Babies with congenital, neurological, cardiovascular anomalies.

- Babies whose mother referred from TORCH infection, HIV, Diabetes mellitus, Pregnancy Induced Hypertension.
- Babies of parents who are not giving consent for this study.
- Babies of irregular follow up during the screening period.
- Babies who did not survive the maximal screening ROP period.

METHODOLOGY:

The various parameters recorded were weight at birth, gestational age , age of postconception, risk factors such as anaemia, long term exposure to oxygen, neonatal jaundice, mechanical ventilation, use of any surfactant , Respiratory Distress Syndrome, sepsis, multiple births ,multiple blood transfusions, , and intraventricular haemorrhage.

Gestational age was calculated according to last menstrual period or according to the date mentioned by first trimester USG abdomen.

In our study the screening protocol for ROP was followed based on the guidelines by National Neonatology Forum (NNF).

The first retinal examination would be held at 4 to 5 weeks from the birth. Retina examined with binocular indirect ophthalmoscope with+20 D lens. Patient information and retinal findings recorded in the ROP screening case sheet.For categorising ROP, revised ICROP guidelines and classification was used. Followup schedule individualised based on the retinal findings and it

would be continued till retina vascularises completely or ROP regression noted or until treated according to the ETROP guidelines.

In our study, “mild ROP” was termed for ROP where the severity not sufficient to meet the criteria for treatment according to “ETROP” and CRYO-ROP study and, “severe ROP” was termed for either the Type 1 ROP based on “ETROP study” findings or the threshold ROP,Agressive ROP, stage 4 ROP(partial RD) or stage 5 ROP(total RD) that validates treatment.

Babies in our study will be categorised into two groups as follows:

GROUP 1: Preterm low birth weight babies with no sepsis(both clinically and culture negative babies)

GROUP 2: Preterm low birth weight babies with sepsis(clinically and culture positive)

Each group would be subdivided into -

- “Severe ROP” babies that necessiates treatment by guidelines of ETROP.
- Babies with no ROP and mild ROP who didn’t meet the criteria for ROP treatment.

The association of babies with both clinical sepsis and culture proven late onset sepsis and the severity of retinopathy of prematurity would be noted and analysed.

PROCEDURE:

- Procedure would be explained to either of the parents or the gaurdian.
- Informed written consent would be obtained.
- Oral feed should be stopped hour prior to the examination preferably.
- Wash hands with disinfectant prior to the procedure.
- Anterior segment of the eye would be examined before retinal examination to look for pupil size ,tunica vasculosa lentis, , pupillary light reflex and lens status.
- Both the eyes are dilated with the mydriatics, a combination of tropicamide 0.5% and phenylephrine 2.5% eye drops which will be prepared by diluting tropicamide 0.8% and phenylephrine 5% eye drop in tear substitutes in 50:50, and used two to three times about 10-15 minutes apart.
- Excess drops would be wiped off to prevent systemic absorption.
- Pupils are dilated fully before the examination. If pupil is not fully dilated, dilatation is to be noted for plus disease.
- Baby placed in examining couch in supine position.
- One drop of topical anaesthetic, 0.5% proparacaine is instilled in culdesac of both the eyes.

- Paediatric universal eye speculum is applied to the eye.
- Retina would be examined by Binocular Indirect Ophthalmoscope Using +20D lens and the retinal periphery is examined using sclera depressor.
- Posterior pole is to be examined for plus disease, followed by orderly examinations of all clock hours of the retinal periphery.
- The retinal findings of ROP will be recorded with the help of fundus diagram using Amsler's color coding.

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STATISTICAL ANALYSIS:

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer by using SPSS 16 software.

Using this software, percentages, means, standard deviations were calculated and 'p' values were calculated from Student 't' test for raw data and chi square test for consolidated data to test the significance of difference between variables.

A 'p' value less than 0.05 is taken to denote significant relationship.

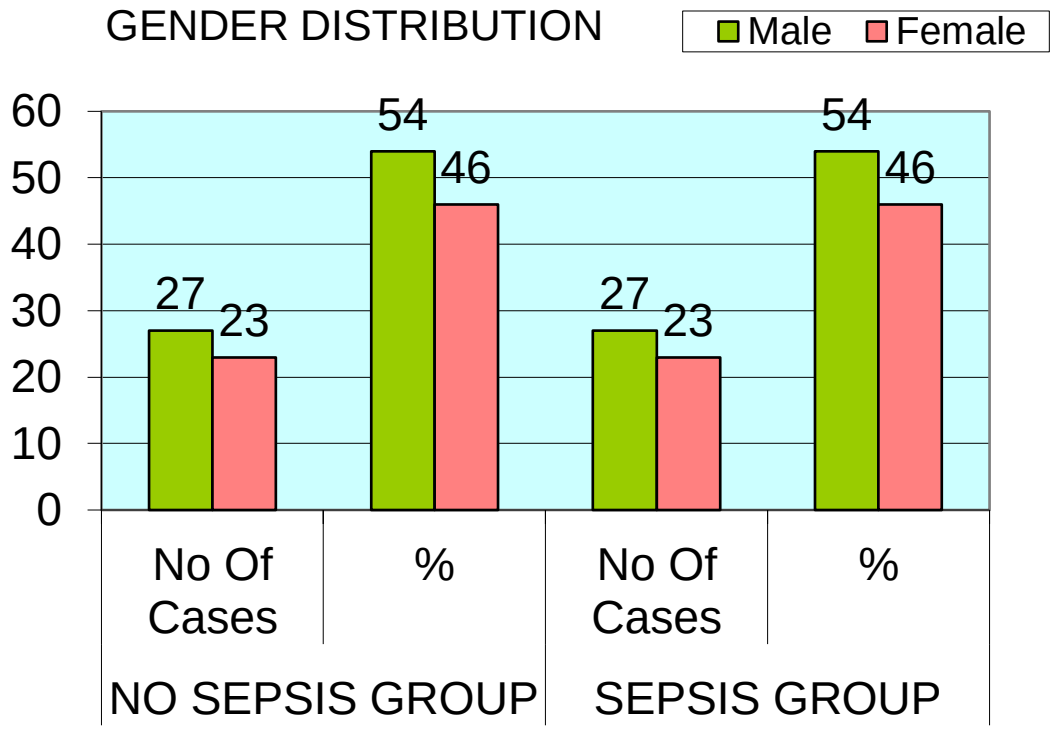
RESULTS:

The study was conducted at our Department of Ophthalmology and Institute of Neonatology in Government Rajaji Hospital, Madurai to assess the assosciation of sepsis with severe ROP. Study was conducted among 100 babies. Babies were divided into two groups bases on the presence of sepsis. So, group 1 contains 50 preterm low birth weight babies with no sepsis and group 2 contains 50 preterm low birth weight babies with sepsis. Severity of ROP was analysed between these groups.

OBSERVATIONAL ANALYSIS

TABLE 1: SEX DISTRIBUTION

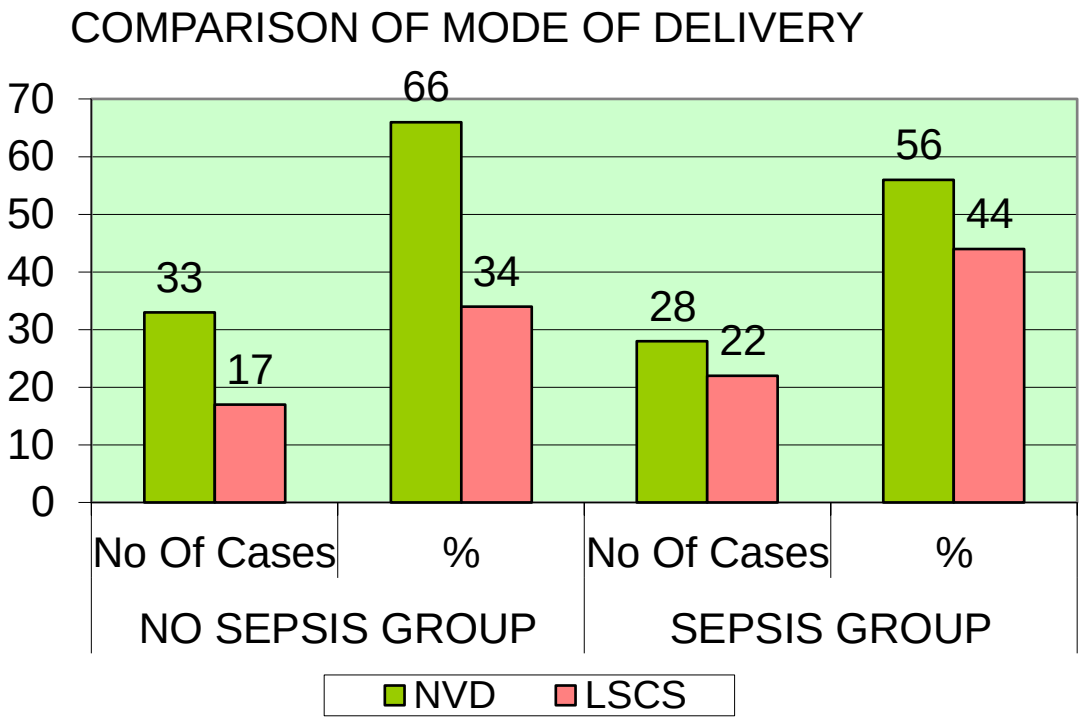
Sex Distribution	NO SEPSIS GROUP		SEPSIS GROUP		Total	P'value
	No Of Cases	%	No Of Cases	%		
Male	27	54	27	54	54	
Female	23	46	23	46	46	
Total	50	100	50	100	100	0.841
						Not significant



Among 100 babies analysed, 54 were males and 46 were females. Group 1 had 27 males and 23 females also Group 2 had 27 males and 23 females. There was no significant association of gender within both the groups, since the ‘p’ value was 0.841.

TABLE2: MODE OF DELIVERY

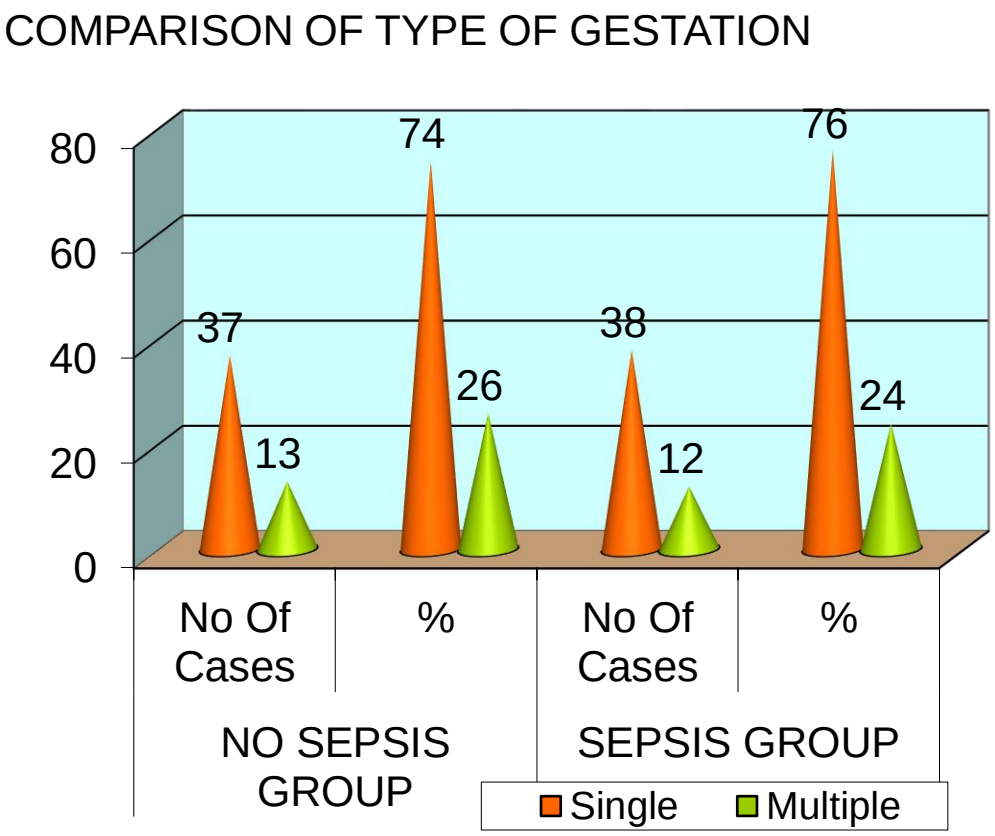
Mode Of Delivery	NO SEPSIS GROUP		SEPSIS GROUP		Total	P'value
	No Of Cases	%	No Of Cases	%		
NVD	33	66	28	56	61	
LSCS	17	34	22	44	39	
Total	50	100	50	100	100	0.412
						Not Significant



Among 100 babies, 61 were normal vaginal delivery and 39 were LSCS. Group 1 had 33 NVD cases and 17 LSCS cases and group 2 had 28 NVD cases and 22 LSCS cases. There was no significant association between two types of mode of delivery in both the groups. (P = 0.412)

TABLE 3: TYPE OF GESTATION

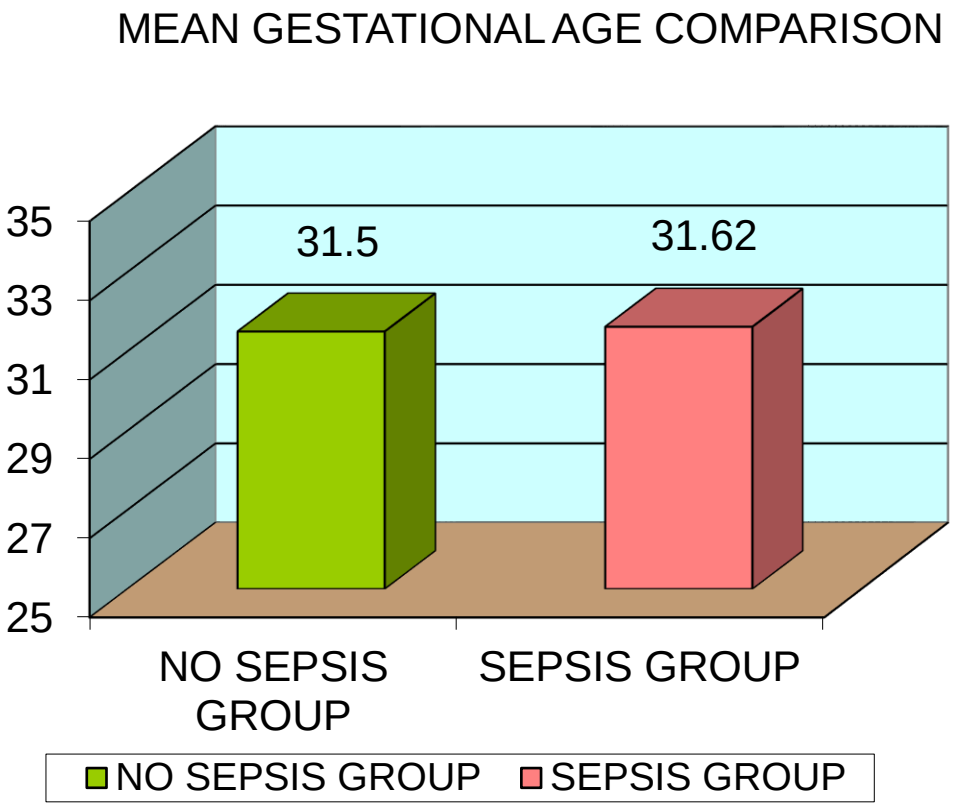
Type Of Gestation	NO SEPSIS GROUP		SEPSIS GROUP		Total	P'value
	No Of Cases	%	No Of Cases	%		
Single	37	74	38	76	75	
Multiple	13	26	12	24	25	
Total	50	100	50	100	100	0.986
						Not significant



Among 100 babies, 75 were single gestation and 25 were twin gestation,Group1 had 37 single gestation babies and 13 twin gestation babies and group 38 single gestation and 12 twin gestation babies. There was no significant difference in type of gestation between two groups.(P = 0.986)

TABLE 4: GESTATIONAL AGE

Gestational Age	Mean	S.D	P'value
NO SEPSIS GROUP	31.5	1.111	
SEPSIS GROUP	31.62	0.945	0.562
			Not significant

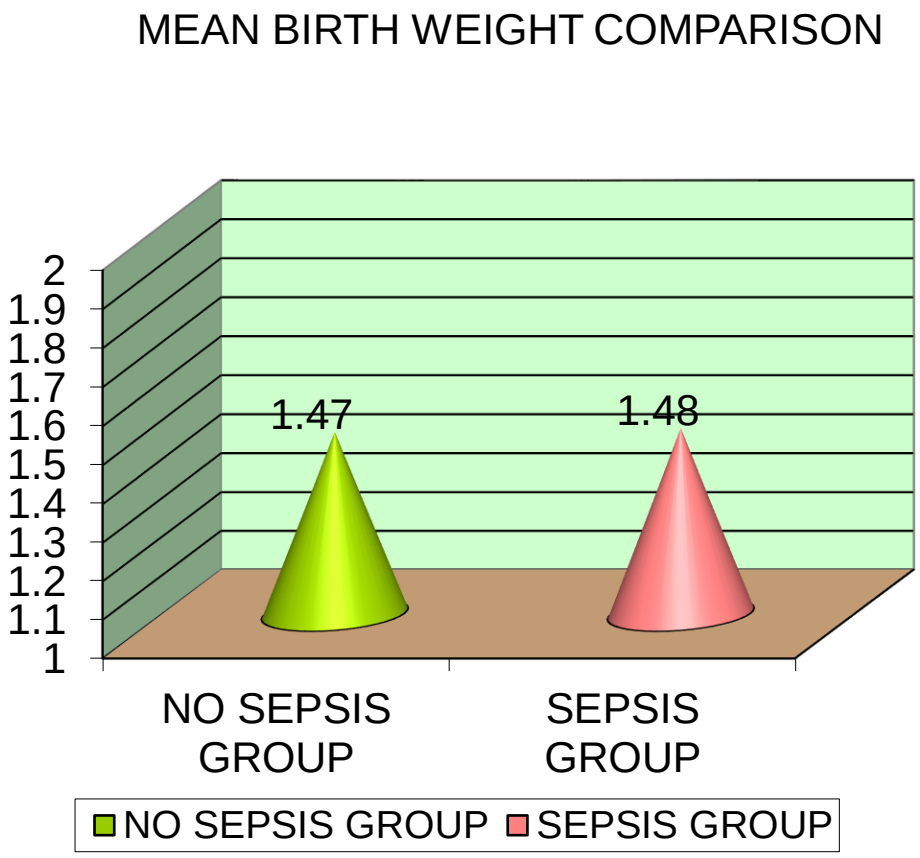


The mean gestational age in group 1 and group 2 were 31.50± 1.11 weeks and 31.62± 0.945 weeks respectively and there is no significant difference in gestational age between 2 groups.(P = 0.562)

TABLE 5: BIRTH WEIGHT

Birth Weight	Mean	S.D	P'value
NO SEPSIS GROUP	1.47	0.133	
SEPSIS GROUP	1.48	0.129	0.703

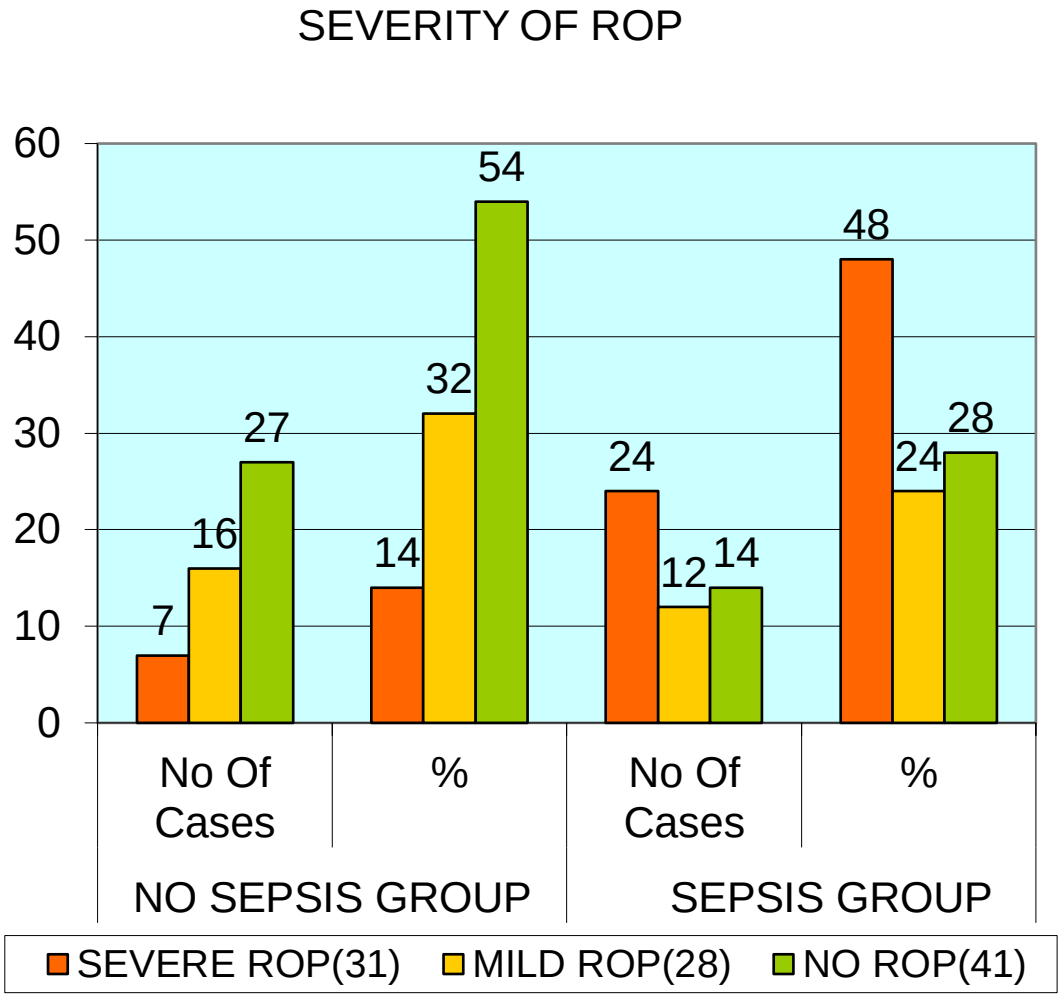
Not significant



The mean birth weight in group 1 and group 2 were 1470.00 ± 0.133 grams and 1480.00 ± 0.129 grams respectively and no significant difference was found between the two groups.(P = 0.703)

TABLE 6: SEVERITY OF ROP

Severity of ROP	NO SEPSIS GROUP		SEPSIS GROUP		
	No Of Cases	%	No Of Cases	%	P'value
SEVERE ROP(31)	7	14	24	48	
MILD ROP(28)	16	32	12	24	
NO ROP(41)	27	54	14	28	<0.001
Total	50	100	50	100	Significant

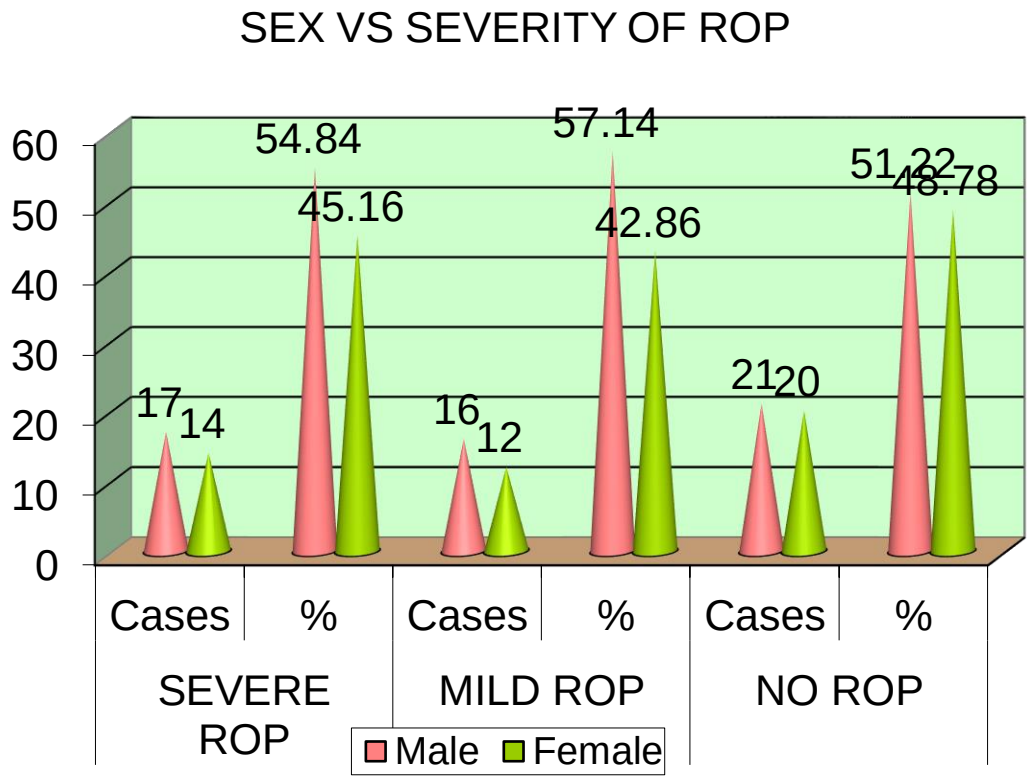


Among 100 babies , 31 were severe ROP cases, 28 mild ROP cases and 41 No ROP cases. Group 1 had 7 severe ROP cases, 16 mild ROP cases, 27 No ROP cases .Group 2 had 24 severe ROP cases,12 mild ROP cases and 14 No ROP cases. The incidence of severe ROP was found to be more among sepsis babies.

Statistical analysis showed, there is significant association between retinal findings in both the groups. (P <0.001).

TABLE 7: SEX DISTRIBUTION AND SEVERITY OF ROP

Sex vs Severity of ROP	SEVERE ROP		MILD ROP		NO ROP		Total	P'value
	Cases	%	Cases	%	Cases	%	Cases	
Male	17	54.84	16	57.14	21	51.22	54	
Female	14	45.16	12	42.86	20	48.78	46	
Total	31	100.00	28	100.00	41	100.00	100	0.884
								Not Significant

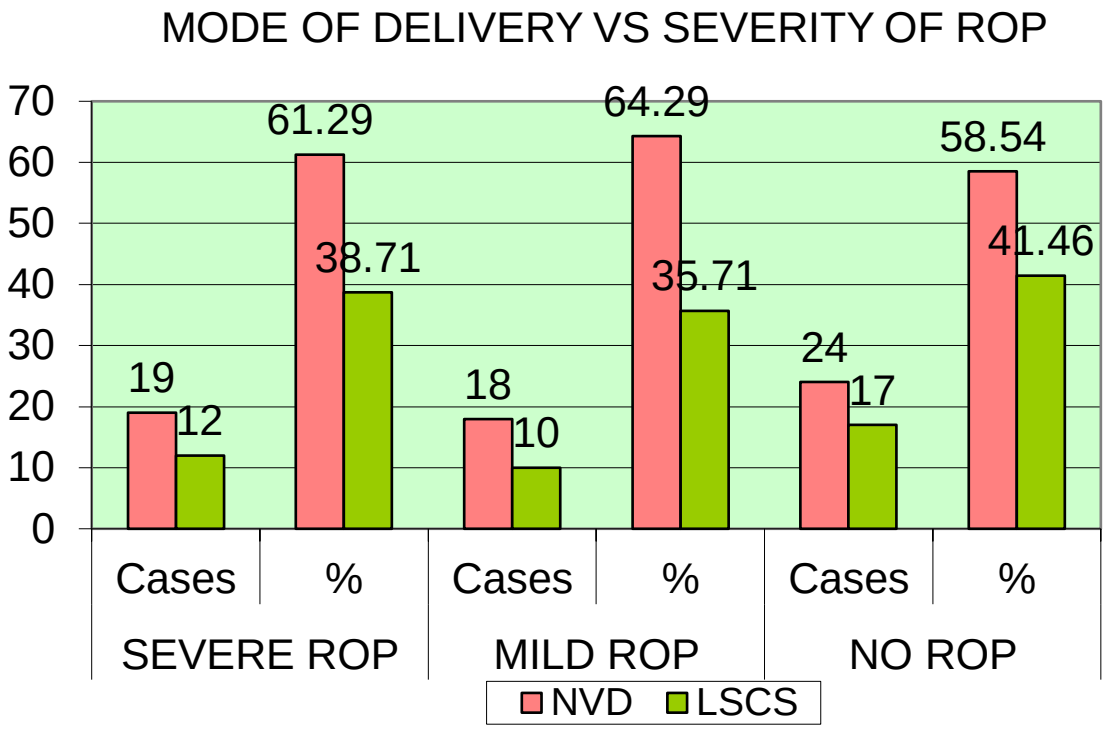


Among 54 male babies, 17 babies had severe ROP,16 babies had mild ROP,21babies had no ROP and among 46 female babies, 14 babies had severe ROP,12 babies had mild ROP, 20 babies had no ROP. There was no significant difference between both the sexes and the retinal findings .P = 0.884

TABLE 8: MODE OF DELIVERY AND SEVERITY OF ROP

Mode Of Delivery vs Severity of ROP	SEVERE ROP		MILD ROP		NO ROP		Total	P'value
	Cases	%	Cases	%	Cases	%	Cases	
NVD	19	61.29	18	64.29	24	58.54	61	
LSCS	12	38.71	10	35.71	17	41.46	39	
Total	31	100.00	28	100.00	41	100.00	100	0.89

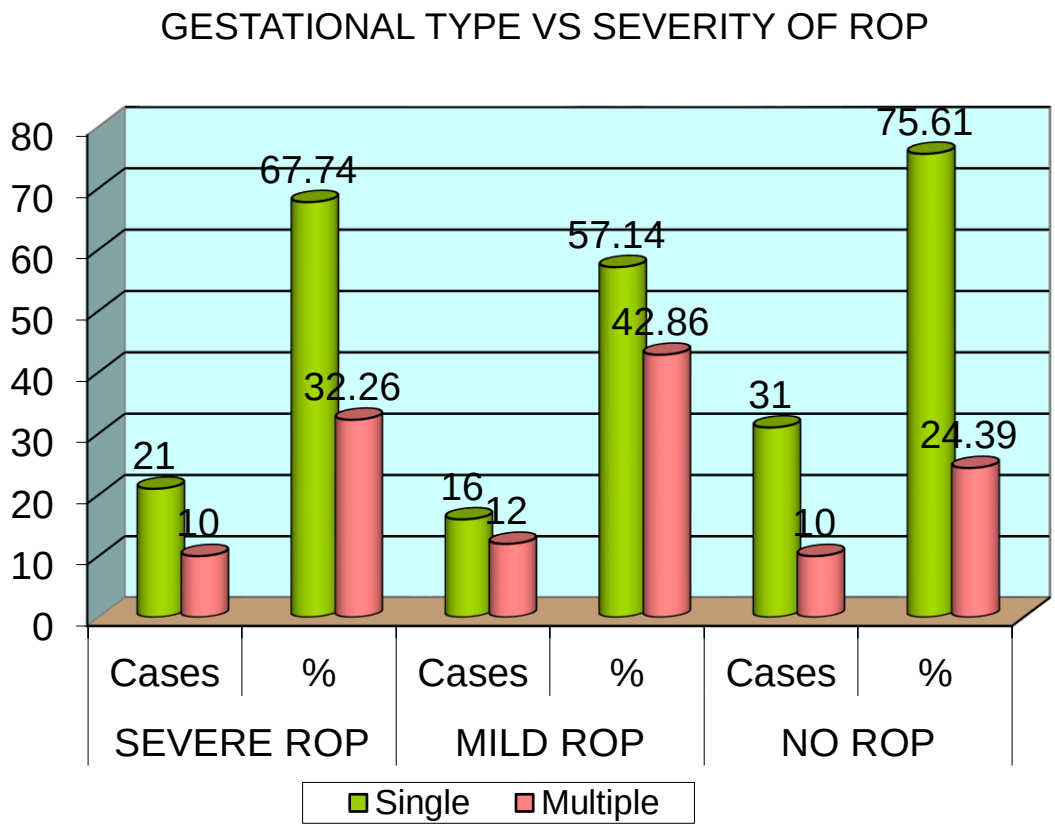
Not Significant



Among 61 normal vaginal delivery cases,19 babies had severe ROP, 18 babies had mild ROP, 24 babies had no ROP and among 39 LSCS cases, 12 babies had severe ROP, 10 babies had mild ROP,17 babies had no ROP. It is found that there is no significant association between mode of delivery and retinal findings, whether it is severe/ mild/ no ROP.(P = 0.890)

TABLE 9: GESTATION AND SEVERITY OF ROP

Gestation Types vs Rational Findings	SEVERE ROP		MILD ROP		NO ROP		Total	P'value
	Cases	%	Cases	%	Cases	%	Cases	
Single	21	67.74	16	57.14	31	75.61	68	
Multiple	10	32.26	12	42.86	10	24.39	32	
Total	31	100.00	28	100.00	41	100.00	100	0.271
								Not Significant



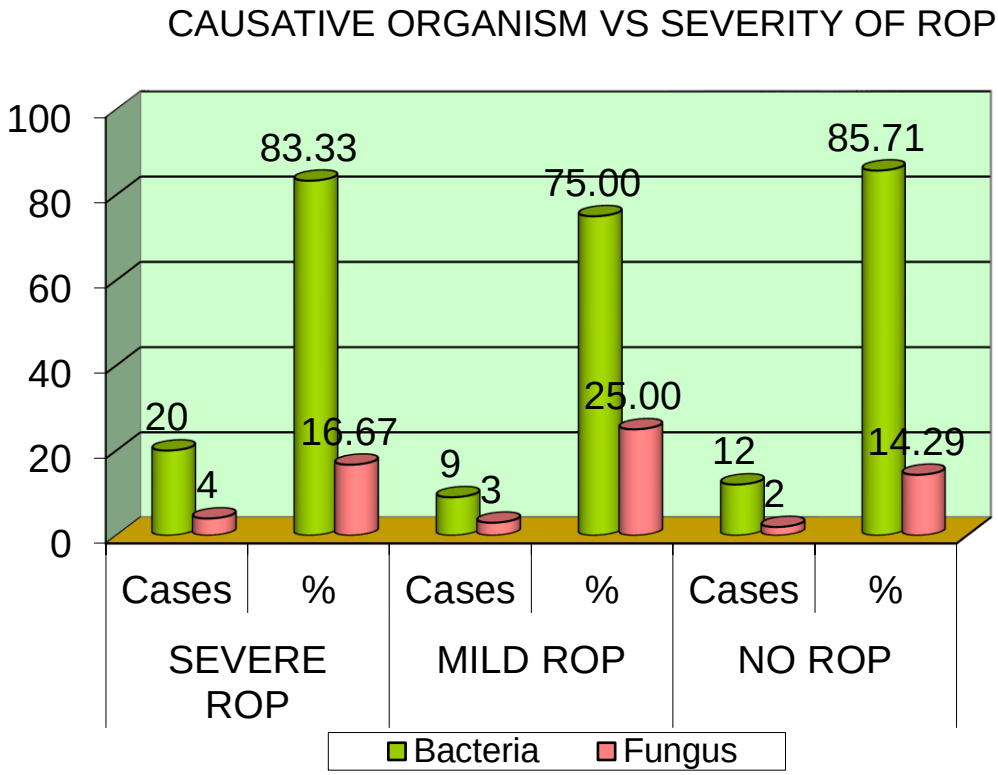
Among 68 single gestation babies,21 babies had severe ROP, 16 babies had mild ROP, 31 babies had no ROP and among 32 twin gestation babies,10 babies had severe ROP, 12 babies had mild ROP and 10 babies had no ROP. There is no significant association between the type of gestation

and retinal findings. (P = 0.271)

TABLE 10: CAUSATIVE ORGANISMS AND SEVERITY OF ROP

Causative organism vs Severity of ROP	SEVERE ROP		MILD ROP		NO ROP		Total	P'value
	Cases	%	Cases	%	Cases	%	Cases	
Bacteria	20	83.33	9	75.00	12	85.71	41	
Fungus	4	16.67	3	25.00	2	14.29	9	0.756
Total	24	100.00	12	100.00	14	100.00	50	

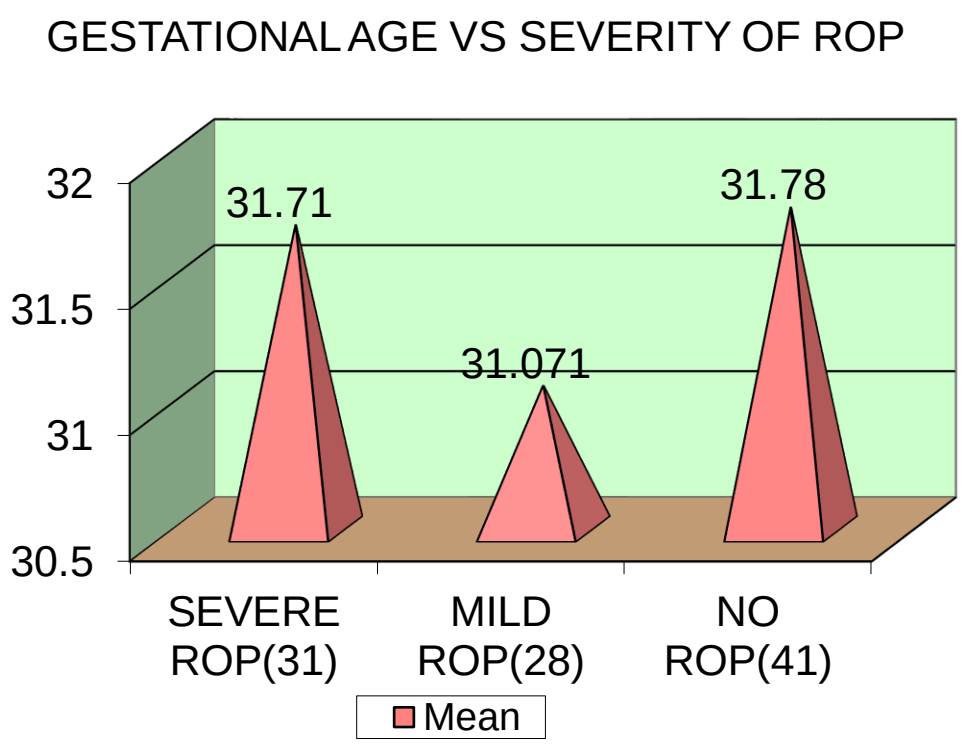
Not Significant



Although the bacterial sepsis(41) was common than fungal sepsis(9) the association of severe ROP between them was not stastically significant ($p = 0.756$).

TABLE 11: GESTATIONAL AGE AND SEVERITY OF ROP

			95% confidence interval for mean		P'value	
Gestational Age vs Severity of ROP	Mean	S.D	Lower Bound	upper Bound		
SEVERE ROP(31)	31.71	0.693	-0.515	0.374	0.752	Not sig
MILD ROP(28)	31.071	1.12	-1.247	-0.171	0.011	Significant
NO ROP(41)	31.78	1.084				

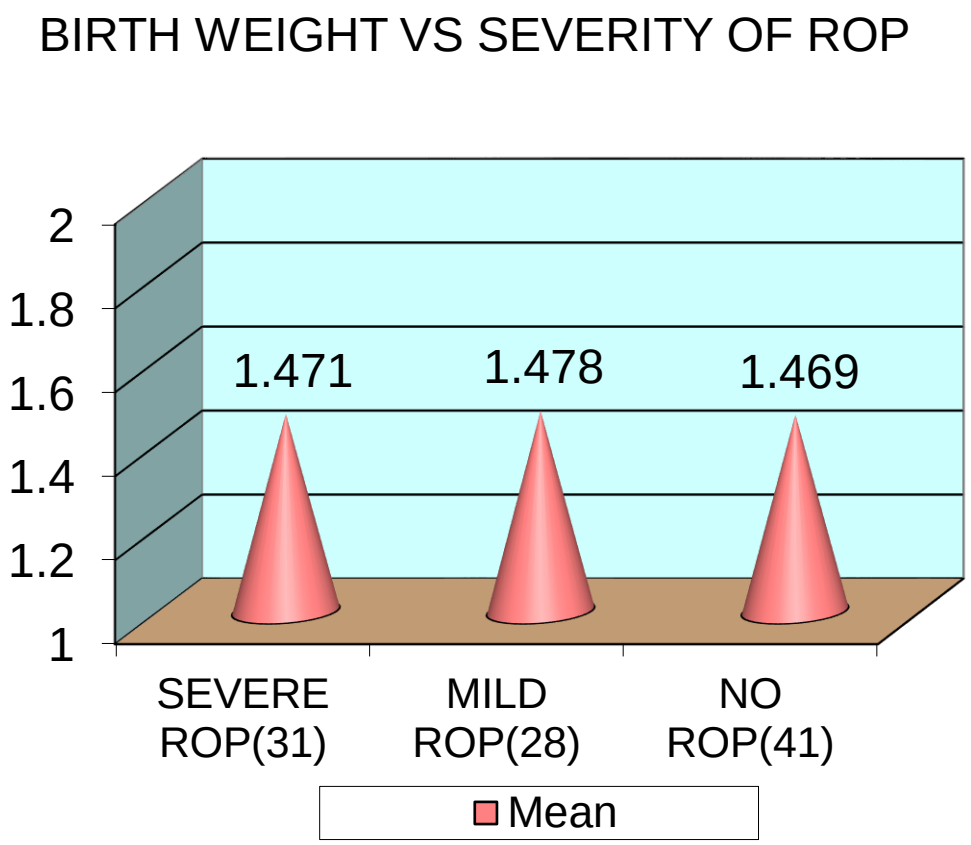


The mean gestational age for severe , mild, no ROP were 31.71±0.693 weeks, 31.07±1.12weeks and 31.78±1.084 weeks respectively and there is no significant difference between gestational age and retinal findings.

TABLE 12: BIRTH WEIGHT AND RETINAL FINDINGS

Birth Weight vs Severity of ROP	Mean	S.D	P'value
SEVERE ROP(31)	1.471	0.117	
MILD ROP(28)	1.478	0.127	
NO ROP(41)	1.469	0.144	0.958

Not significant



The mean birth weight for severe, mild, no ROP were 1471.00±117.00grams, 1478.00±127.00 grams and 1469.00±144.00 grams respectively and no significant difference was found between birth weight and retinal findings.

SUMMARY OF RESULTS:

- Among 100 babies whom were under the study , 31 had severe ROP , 28 had mild ROP and 41 had No ROP .
- Among 100 babies analysed , 54 were males and 46 were females. Group 1 had 27 males and 23 females also Group 2 had 27 males and 23 females. There was no significant association of gender within both the groups, since the 'p' value was 0.841.
- The mean gestational age in group 1 and group 2 were 31.50± 1.11 weeks and 31.62± 0.945 weeks respectively and there is no significant difference in gestational age between 2 groups.(P = 0.562)
- The mean birth weight in group 1 and group 2 were 1470.00 ± 0.133 grams and 1480.00 ± 0.129 grams respectively and no significant difference was found between the two groups.(P = 0.703)
- Among 100 babies, 61 were normal vaginal delivery and 39 were LSCS. Group 1 had 33 NVD cases and 17 LSCS cases and group 2 had 28 NVD cases and 22 LSCS cases. There was no significant association between two types of mode of delivery in both the groups. (P = 0.412)
- Among 54 male babies, 17 babies had severe ROP,16 babies had mild ROP,21babies had no ROP and among 46 female babies, 14 babies had severe ROP,12 babies had mild ROP, 20 babies had no ROP. There was no significant difference between both the sexes and the retinal findings .P = 0.884

- Among 61 normal vaginal delivery cases,19 babies had severe ROP, 18 babies had mild ROP, 24 babies had no ROP and among 39 LSCS cases, 12 babies had severe ROP, 10 babies had mild ROP,17 babies had no ROP. It is found that there is no significant association between mode of delivery and retinal findings, whether it is severe/ mild/ no ROP. (P = 0.890)
- In this study, bacterial sepsis(41) was noted to be higher than the fungal sepsis(9) .The association of severe ROP between them was not stastically significant(p = 0.756).
- The mean gestational age for severe , mild, no ROP were 31.71±0.693 weeks, 31.07±1.12weeks and 31.78±1.084 weeks respectively and there is no significant difference between gestational age and retinal findings.
- The mean birth weight for severe, mild, no ROP were 1471.00±117.00grams, 1478.00±127.00 grams and 1469.00±144.00 grams respectively and no significant difference was found between birth weight and retinal findings.
- Among 31severe ROP babies, Group 1 had 7 severe ROP cases, Group 2 had 24 severe ROP cases. The incidence of severe ROP was found to be more among sepsis babies. Statistical analysis showed, there is significant association between retinal findings in both the groups. (P <0.001).

As this study shows a significant association between sepsis and

severe retinopathy of prematurity, sepsis should be consider as an important risk factor for ROP .

DISCUSSION:

- Retinopathy Of Prematurity (ROP) is an abnormal retinal vascular development that occurs in the postnatal period. Hence identifying the postnatal risk fctors which have a predictive value in development and severity of ROP will be helpful for screening, diagnosing and treaing the ROP timely.
- Timely intervention of ROP will favour the visual outcome by avoiding the ROP sequeale.
- ROP being one of the leading cause of blindness among children, is a disease of the developing retinal vasculature . The pathogenesis in ROP is the disturbance of relative hypoxic state which is essential for normal vascular growth. In ROP there is an imbalance between hypoxia-hyperoxia state leading to the growth of abnormal vessels.
- Hypoxia followed by hyperoxic state leads to a proliferative phase, which results as a consequence of alterations in the level of local vascular endothelial growth factor (VEGF) and the systemic insulin-like growth factor 1 (IGF-1). In normal state,VEGF is a vasoproliferative factor needed for the growth of retinal vessels and endothelial cell survival.
- However, VEGF can promote vessel growth only in combination with sufficient serum levels of IGF-1 which is deficient in premature infants

due to lack of maternal sources. Therefore, VEGF starts to accumulate as the metabolic demand of the retina increases. As the age and size of the baby increases, endogenous production of IGF-1also rises, thus promoting the VEGF activity and ultimately proliferative retinopathy develops as a result of highly accumulated VEGF.

- Recently, sepsis have been reported to play an important role in ROP. Infectious organisms or the proinflammatory cytokines mainly TNF-alpha stimulates VEGF production. Imbalance in the production of reactive oxygen species and antioxidant defences during sepsis also leads to sepsis.
- Fluctuation in oxygen saturation following sepsis due to unstable cardiac or respiratory status affects the retinal perfusion leading to retinal ischaemia and subsequently ROP.
- Baley JE et al published the association of ROP and fungal sepsis in very low birth weight babies. They concluded that fungal colonisation in very low birth weight babies act as a important risk factor for ROP. In our study the number of babies suffered from bacterial sepsis was higher than those suffered from fungal sepsis. But the association of severe ROP was not stastically significant between the two group.
- Stoll BJ et al conducted study about ROP and late onset sepsis in very low birth weight babies. They concluded positive association between

the above two factors. In our study the population include babies with late onset sepsis and those with low gestational age and low birth weight. In our study also, low birth weight babies with late onset sepsis had severe ROP which is stastically significant.

- ROP if advances, it would be a visually devastating disorder ending up in permanent visual disability. Hence ROP warrants early detection and timely treatment.
- Premature babies when admitted in NICU for sepsis, it should be consider as an alarming risk factor and the babies should be closely followed up. Parents should be educated on ROP and should be advised for timely and regular follow up.
- As sepsis is associated with devastating ocular complications,its prevention should be started antenatally by educating the mother about the importance of breast feeding, cleanliness, cord care, hospital delivery,etc.,
- Karlowicz et al published on " Does candidemia predict threshold retinopathy of prematurity in extremely low birth weight neonates?".In their study candidemia had a positive association with threshold ROP.
- Our study necessitates the periodic follow up in premature babies with sepsis either bacteria or fungal in etiology, even without the presence of the other risk factors. This will help in prompt case detection and to

deliver the optimal treatment for ROP thus reducing the overall burden of childhood blindness.

- Our study included babies whom were referred from NICU as treated for culture positive late onset sepsis. We were on lack of detailed information on sepsis such as factor that causes sepsis, presentation of sepsis or the system affected, duration of sepsis and the time and duration of treatment received.

This approach will help reduce the number of infants to undergo stressful eye examination for ROP and also for precisely targeting on the babies at risk of developing severe ROP. This method also emphasis on more regulated follow up schedule for babies with high risk. By ensuring the visit compliance, so that unfavourable outcomes from the missed ROP appointments can be avoided.

- Newer treatment modalities aiming to improve the physiologic retinal vascularisation such as supplemention of erythropoietin, IGF-1, omega 3 polyunsaturated fatty acid have shown good results in animal studies, but it needs more work up to implement in preterm infants.
- Recently many randomized clinical trials have found out an essential nutrient –“ inositol” which helps to reduce the severity of ROP.

CONCLUSION:

- Our study showed that late onset sepsis is strongly associated with severe ROP that warrants immediate treatment by ETROP guidelines. When sepsis is present in preterm low birth weight babies, it should be considered as an independent risk factor for ROP.
- When sepsis babies are screened for ROP regularly, it will help to detect the ROP timely and treatment can be delivered at its earliest. Thus reducing the devastating sequeale of ROP. It is also helpful to avoid unnecessary stressful examination on preterm infants who are not at risk of developing “severe ROP”.
- Our study result emphazises the ophthalmologists and the neonatologists to have more attention and special care to those babies with sepsis to predict and diagnose the disease much earlier before it is being diagnosed by the regular ophthalmic examination .It will help to intervene early and to prevent sight threatening complications.

ANNEXURES

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PROFOMA:

Name of the Baby	:	Date of screening	:
Gender	:	Address	:
Postnatal age	:	OP / IP Number	:
Name of the parent	:	Birth place	:
Single/multiple births:		BLOOD CULTURE:	
		Site 1 :	
DOB	:	Site 2 :	
Birth weight	:		
LMP	:		
EDD	:		

Gestational age at Birth:

Postconceptional age :

Delivery mode :

Gestational code :

Maternal factors : Anaemia/ PIH / Diabetes/HIV/ TORCH/PROM/Others

If others:

Fetal risk factors : Sepsis/ Blood transfusions/ phototherapy/ Thrombocytopenia

Mechanical ventilation/ CPAP/ Oxygen supplements/Others

If others:

Systemic examination : CVS:

RS:

CNS:

OCULAR EXAMINATION:

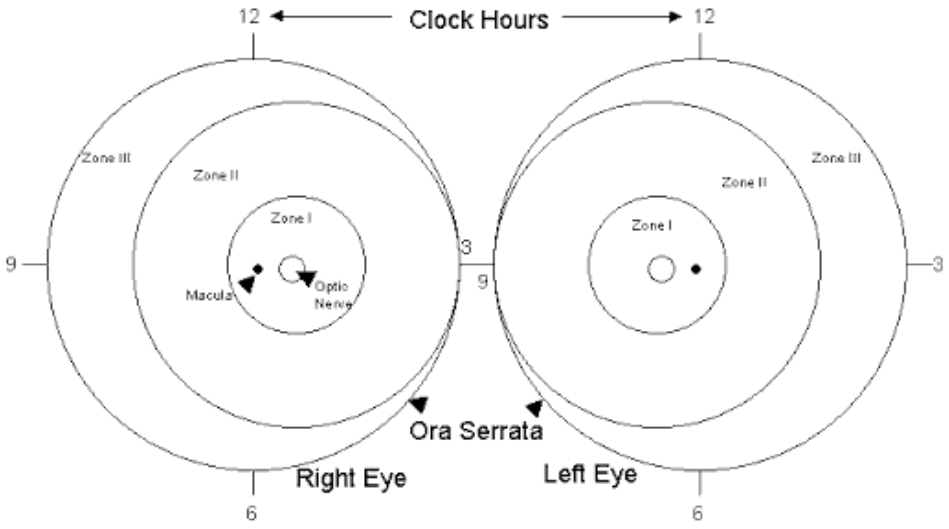
ANTERIOR SEGMENT

OD		OS
	Lids	
	Conjunctiva	
	Cornea Diameter Transparency	
	Anterior chamber	
	Iris	
	Pupil Size Color	
	Lens	

POSTERIOR SEGMENT

OD		OS
	Media	
	Disc	
	Retinal vessels	
	ROP-Zone,Stage	
	Clock hours involved	
	Fovea	
	Plus disease	

Fundus diagram:

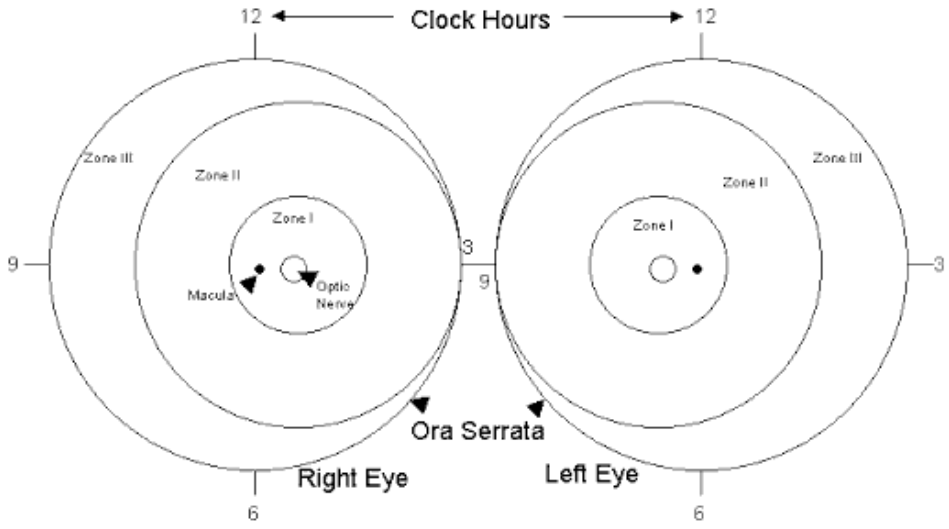


Diagnosis:

Treatment planned:

Follow-up advice:

Follow up details: No. of visit/ Date

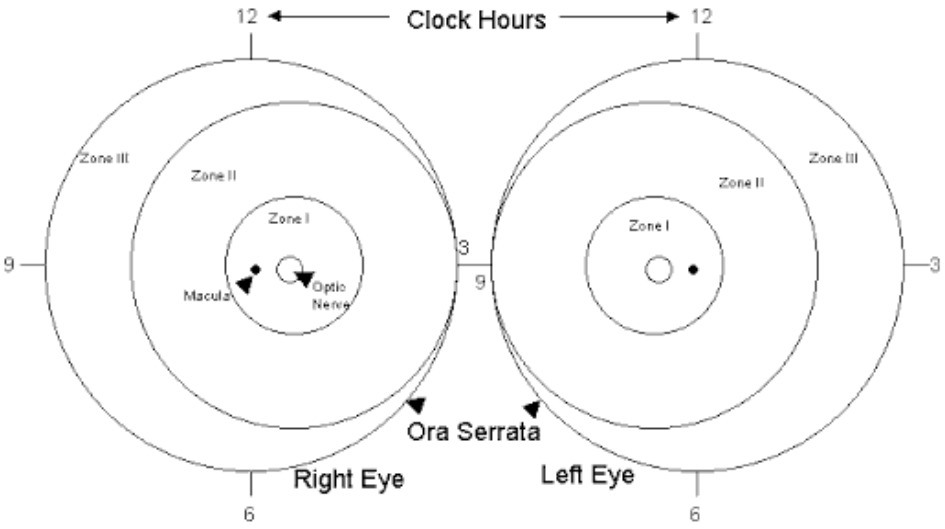


Diagnosis:

Treatment Planned:

Followup advice:

Follow up details: No.of visit/ Date

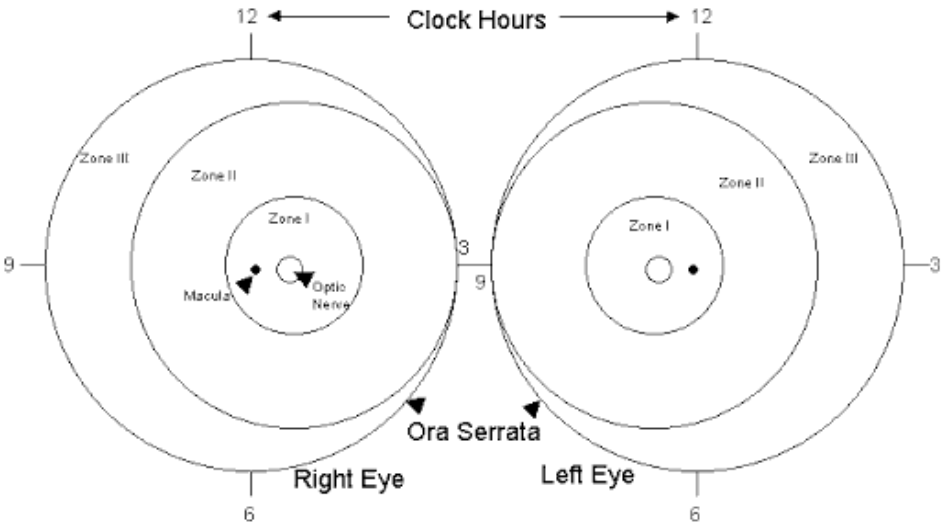


Diagnosis:

Treatment Planned:

Followup advice:

Follow up details: No.of visit/ Date

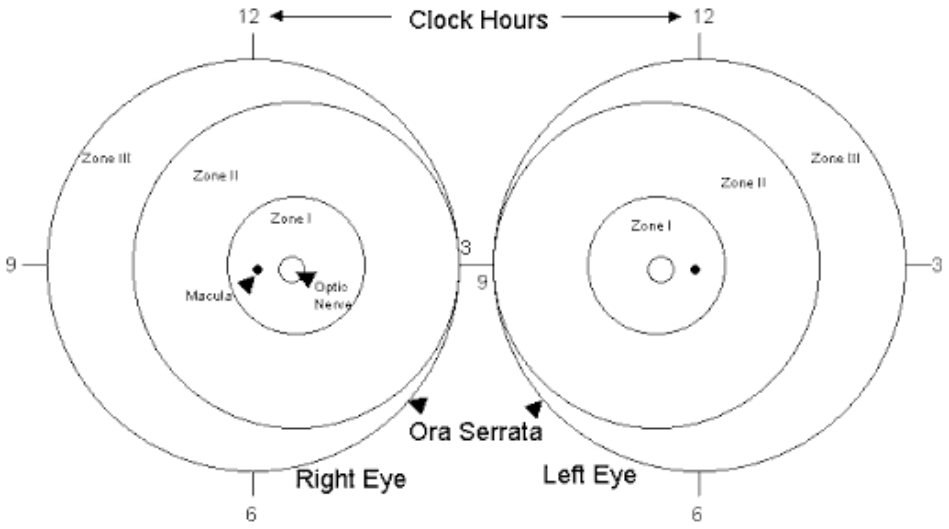


Diagnosis:

Treatment Planned:

Followup advice:

Follow up details: No.of visit/ Date



Diagnosis:

Treatment Planned:

Followup advice:

MASTER CHART

S.NO	NAME	GESTATIONAL AGE (WEEKS)	BIRTH WEIGHT (KG)	SEX	MODE OF DELIVERY	TYPE OF GESTSTION	MATERNAL RISK FACTORS	FETAL RISK FACTORS OTHER THAN SEPSIS	SEPSIS			RETINAL FINDINGS		
									NO SEPSIS	BACTERIAL	FUNGAL	NO ROP	MILD ROP	SEVERE ROP
1	Harshini	32	1.57	F	NVD	Single	_	_	_	BACTERIAL	_	_	_	SEVERE ROP
2	Raghavan	32	1.44	M	NVD	Single	_	RDS/Anaemia	_	BACTERIAL	_	_	_	SEVERE ROP
3	B/o sasikala	31	1.7	F	LSCS	Single	_	RDS	_	BACTERIAL	_	_	_	SEVERE ROP
4	B/o karunya	32	1.4	M	LSCS	Single	_	Neonatal jaundice	_	BACTERIAL	_	_	_	SEVERE ROP
5	B/o parameshwari	33	1.69	F	NVD	Single	_	HIE	_	BACTERIAL	_	NO ROP	_	_
6	B/o Sundari	31	1.55	F	LSCS	Twin	_	Neonatal jaundice	_	BACTERIAL	_	NO ROP	_	_
7	B/o maninegalai	30	1.38	M	NVD	Twin	_	RDS	_	_	FUNGAL	_	MILD ROP	_
8	B/o Sundari	32	1.42	M	LSCS	Single	_	_	_	BACTERIAL	_	NO ROP	_	_
9	B/o Rani	31	1.63	F	LSCS	Twin	_	Anaemia	_	**BACTERIAL**	_	_	MILD ROP	_
10	B/0 Rithik	30	1.44	M	NVD	Single	_	HIE	_	BACTERIAL	_	_	MILD ROP	_
11	**B**/o Vijayalakshmi	32	1.32	M	NVD	Single	_	_	_	BACTERIAL	_	_	MILD ROP	_
12	B/o jagadeeswari	31	1.25	F	NVD	Single	_	IUGR/Neonatal depression	_	BACTERIAL	_	_	_	SEVERE ROP
13	B/o sabmunika	32	1.42	M	LSCS	Single	_	_	_	_	FUNGAL	_	_	SEVERE ROP
14	Dhamoorthi	30	1.53	F	LSCS	Twin	_	RDS/Anaemia	_	BACTERIAL	_	_	MILD ROP	_

15	Sabhunda	33	1.32	F	NVD	Single	_	_	_	BACTERIAL	_	NO ROP	_	_
16	B/o Raji	32	1.42	M	NVD	Single	_	HIE	_	BACTERIAL	_	_	_	SEVERE ROP
17	B/o suganya	33	1.69	M	LSCS	Single	_	Meconium stained amniotic fluid	_	BACTERIAL	_	NO ROP	_	_
18	b/O Nagalakshmi	31	1.53	F	LSCS	Twin	_	RDS	_	BACTERIAL	_	_	_	SEVERE ROP
19	B/o chinnu	33	1.63	F	NVD	Single	_	_	_	BACTERIAL	_	_	MILD ROP	_
20	B/o divya	33	1.55	M	NVD	Twin	_	_	_	_	FUNGAL	_	_	SEVERE ROP
21	B/o muthupechi	31	1.32	M	LSCS	Single	_	Neonatal jaundice	_	BACTERIAL	_	NO ROP	_	_
22	B/o Rajalakshmi	32	1.45	M	NVD	Single	_	_	_	BACTERIAL	_	_	_	SEVERE ROP
23	B/o Sumathi	30	1.36	F	NVD	Single	_	Anaemia	_	BACTERIAL	_	_	MILD ROP	_
24	B/o Muthumari	32	1.52	F	LSCS	Twin	_	_	_	BACTERIAL	_	_	MILD ROP	_
25	kannan	31	1.39	M	NVD	Single	_	Neonatal jaundice	_	BACTERIAL	_	_	_	SEVERE ROP
26	B/o Uma maheswari	31	1.46	F	LSCS	Single	_	_	_	_	FUNGAL	_	_	SEVERE ROP
27	B/o kaniskadevi	32	1.38	F	LSCS	Single	_	_	_	BACTERIAL	_	NO ROP	_	_
28	B/o Vijayalakshmi	33	1.32	M	NVD	Single	_	_	_	BACTERIAL	_	_	_	SEVERE ROP
29	B/o meenakshi	30	1.7	M	NVD	Twin	_	Neonatal jaundice/Surfactant	_	BACTERIAL	_	_	MILD ROP	_
30	B/o Kamali	32	1.56	F	LSCS	Single	_	Birth asphyxia	_	BACTERIAL	_	NO ROP	_	_
31	B/o Mahalakshmi	30	1.43	M	NVD	Single	_	RDS	_	_	FUNGAL	_	MILD ROP	_
32	B/o Vijayalakshmi	33	1.58	F	LSCS	Single	_	_	_	_	FUNGAL	_	_	SEVERE ROP
33	Ganesh	32	1.32	M	LSCS	Twin	_	Neonatal jaundice	_	BACTERIAL	_	_	_	SEVERE ROP
34	B/o poongodhai	31	1.67	F	NVD	Single	_	Neonatal jaundice	_	BACTERIAL	_	NO ROP	_	_

35	B/o muthukumari	32	1.25	M	NVD	Single	_	_	_	BACTERIAL	_	_	MILD ROP	_
36	B/o perumayee	33	1.56	M	LSCS	Single	_	_	_	_	FUNGAL	NO ROP	_	_
37	B/o maruthayee	32	1.44	M	LSCS	Single	_	Rh incompatibility	_	BACTERIAL	_	NO ROP	_	_
38	B/o Nagasri	31	1.36	F	NVD	Single	_	RDS	_	BACTERIAL	_	_	_	SEVERE ROP
39	B/o Elizabeth	32	1.508	M	LSCS	Twin	_	RDS	_	_	FUNGAL	_	MILD ROP	_
40	Manisha	30	1.33	F	NVD	Single	_	Neonatal jaundice	_	BACTERIAL	_	NO ROP	_	_
41	Krishnavandh	33	1.722	M	NVD	Single	_	_	_	_	FUNGAL	NO ROP	_	_
42	B/o Manjula	32	1.47	M	LSCS	Single	_	HIE	_	BACTERIAL	_	NO ROP	_	_
43	Mahalakshmi	31	1.52	F	NVD	Twin	_	Birth asphyxia	_	BACTERIAL	_	_	_	SEVERE ROP
44	B/o Thiruveni	32	1.62	M	NVD	Single	_	HIE/Neonatal jaundice	_	BACTERIAL	_	_	_	SEVERE ROP
45	B/o Athilakshmi	32	1.54	F	LSCS	Single	_	_	_	BACTERIAL	_	_	_	SEVERE ROP
46	Sudeshika	31	1.62	M	NVD	Single	_	Neonatal jaundice	_	BACTERIAL	_	_	_	SEVERE ROP
47	B/oDeepika	32	1.44	F	NVD	Twin	_	HIE	_	BACTERIAL	_	_	_	SEVERE ROP
48	Adhidevi	31	1.26	M	LSCS	Single	_	Surfactant	_	BACTERIAL	_	_	_	SEVERE ROP
49	B/o Sudha	31	1.42	M	NVD	Single	_	Birth asphyxia	_	BACTERIAL	_	_	_	SEVERE ROP
50	B/o Amudhalakshmi	32	1.44	F	NVD	Single	_	Neonatal jaudice	_	BACTERIAL	_	_	_	SEVERE ROP
51	B/o Sathya	33	1.5	M	LSCS	Twin	_	Anaemia	NO SEPSIS	_	_	NO ROP	_	_
52	B/o juliet	31	1.2	M	NVD	Single	_	NNJ	NO SEPSIS	_	_	NO ROP	_	_
53	B/o Niveditha	33	1.4	F	NVD	Single	_	Birth asphyxia	NO SEPSIS	_	_	NO ROP	_	_
54	B/o Lalitha	31	1.3	M	LSCS	Twin	_	NNJ	NO SEPSIS	_	_	_	MILD ROP	_

55	B/o Dhanalakshmi	32	1.43	M	NVD	Single	_	HIE	NO SEPSIS	_	_	_	MILD ROP	_
56	B/o Sasikala	30	1.32	F	NVD	Single	_	_	NO SEPSIS	_	_	NO ROP	_	_
57	B/o Kaliammal	32	1.44	M	LSCS	Single	_	Neonatal jaundice	NO SEPSIS	_	_	_	_	SEVERE ROP
58	B/o poongodhai	31	1.29	M	NVD	Twin	_	Anaemia	NO SEPSIS	_	_	_	MILD ROP	_
59	B/o Gayathri	32	1.36	F	NVD	Single	_	HIE	NO SEPSIS	_	_	NO ROP	_	_
60	B/o Radhika	33	1.27	M	LSCS	Single	_	_	NO SEPSIS	_	_	NO ROP	_	_
61	B/o Bharathi	29	1.42	M	NVD	Single	_	Birth asphyxia	NO SEPSIS	_	_	NO ROP	_	_
62	B/o Sathya	32	1.56	F	LSCS	Twin	_	_	NO SEPSIS	_	_	_	MILD ROP	_
63	B/o Lakshmi	31	1.54	M	NVD	Single	_	HIE	NO SEPSIS	_	_	_	_	SEVERE ROP
64	B/o Dhivya	33	1.47	F	LSCS	Single	_	Anaemia/PL	NO SEPSIS	_	_	NO ROP	_	_
65	B/o Pandimeena	30	1.36	M	NVD	Twin	_	Neonatal jaundice	NO SEPSIS	_	_	_	MILD ROP	_
66	B/o meenakshi	32	1.42	F	NVD	Single	_	HIE	NO SEPSIS	_	_	NO ROP	_	_
67	B/o Vanitha	31	1.64	M	LSCS	Twin	_	_	NO SEPSIS	_	_	NO ROP	_	_
68	B/O Selvi	31	1.57	F	NVD	Single	_	_	NO SEPSIS	_	_	_	MILD ROP	_
69	B/o Sindhuja	33	1.43	M	NVD	Single	_	HIE	NO SEPSIS	_	_	NO ROP	_	_
70	B/o Kavitha	32	1.66	F	NVD	Single	_	Anaemia/WB	NO SEPSIS	_	_	_	MILD ROP	_
71	B/o Deepa	31	1.61	M	LSCS	Single	_	HIE	NO SEPSIS	_	_	NO ROP	_	_
72	B/o Kaleeswari	33	1.58	F	NVD	Twin	_		NO SEPSIS	_	_	_	_	SEVERE ROP
73	B/o Amaravathy	30	1.36	M	NVD	Single	_	Neonatal jaundice	NO SEPSIS	_	_	NO ROP	_	_
74	B/o Saranya	31	1.42	F	NVD	Single	_	HIE	NO SEPSIS	_	_	NO ROP	_	_

75	B/o Gandhimadhi	29	1.55	M	NVD	Single	_	Anaemia/WB	NO SEPSIS	_	_	_	MILD ROP	_
76	B/o Niraimathi	33	1.29	M	NVD	Twin	_	Birth asphyxia	NO SEPSIS	_	_	NO ROP	_	_
77	B/o Sathya	32	1.43	F	NVD	Single	_	_	NO SEPSIS	_	_	NO ROP	_	_
78	B/o Alagulakshmi	31	1.46	M	LSCS	Single	_	HIE	NO SEPSIS	_	_	NO ROP	_	_
79	B/o Karthiga	31	1.53	F	NVD	Single	_	_	NO SEPSIS	_	_	_	MILD ROP	_
80	B/o meena	30	1.47	M	LSCS	Twin	_	Neonatal jaundice	NO SEPSIS	_	_	_	MILD ROP	_
81	B/o Alagumeena	31	1.64	F	NVD	Single	_	_	NO SEPSIS	_	_	NO ROP	_	_
82	B/o Rakku	33	1.58	M	NVD	Single	_	HIE	NO SEPSIS	_	_	NO ROP	_	_
83	B/o Aruna	32	1.38	F	NVD	Single	_	Neonatal jaundice	NO SEPSIS	_	_	NO ROP	_	_
84	B/o Pandimeena	31	1.54	M	LSCS	Twin	_	_	NO SEPSIS	_	_	_	MILD ROP	_
85	B/o Shantimathi	30	1.45	F	NVD	Single	_	HIE	NO SEPSIS	_	_	NO ROP	_	_
86	B/o Sobanadevi	32	1.56	M	LSCS	Single	_	Neonatal jaundice/FFP	NO SEPSIS	_	_	NO ROP	_	_
87	B/o Indhu	33	1.48	F	NVD	Single	_	HIE	NO SEPSIS	_	_	_	MILD ROP	_
88	B/o Dhivya bharathi	32	1.55	M	NVD	Single	_	Birth asphyxia	NO SEPSIS	_	_	_	_	SEVERE ROP
89	B/o Nandhini	31	1.34	F	NVD	Single	_	_	NO SEPSIS	_	_	NO ROP	_	_
90	B/o Nandhini	32	1.38	M	LSCS	Single	_	Birth asphyxia	NO SEPSIS	_	_	NO ROP	_	_
91	B/o Rajalakshmi	31	1.28	F	NVD	Twin	_	Meconium stained amniotic fluid	NO SEPSIS	_	_	NO ROP	_	_
92	B/o Sathyapriya	32	1.46	F	NVD	Single	_	_	NO SEPSIS	_	_	_	MILD ROP	_
93	B/o Murugeshwari	30	1.66	M	LSCS	Single	_	_	NO SEPSIS	_	_	_	MILD ROP	_
94	B/o Kaleeswari	33	1.68	F	NVD	Single	_	Birth asphyxia	NO SEPSIS	_	_	NO ROP	_	_

95	B/o Kalaiarasi	31	1.44	M	LSCS	Twin	_	HIE	NO SEPSIS	_	_	_	_	SEVERE ROP
96	B/0 Rithika	32	1.32	F	NVD	Single	_	Neonatal jaundice	NO SEPSIS	_	_	_	_	SEVERE ROP
97	B/o Divya bharathi	33	1.56	M	NVD	Single	_	Neonatal jaundice/FFP	NO SEPSIS	_	_	_	MILD ROP	_
98	B/o Anandhi	31	1.7	F	LSCS	Single	_	HIE	NO SEPSIS	_	_	_	_	SEVERE ROP
99	B/o Pandeeswari	32	1.8	M	NVD	Twin	_	HIE	NO SEPSIS	_	_	NO ROP	_	_
100	B/o Sindhuja	30	1.26	F	LSCS	Single	_	Birth asphyxia	NO SEPSIS	_	_	_	MILD ROP	_

KEYS TO MASTER CHART

GA	GESTATIONAL AGE
BW	BIRTH WEIGHT
RDS	RESPIRATORY DISTRESS SYNDROME
O_2	OXYGEN
CPAP	CONTINOUS POSTIVE AIRWAY PRESSURE
SIMV	SYNCHRONISED INTERMITTENT MECHANICAL VENTILATION
LSCS	LOWER SEGMENT CAESERIAN SECTION
NVD	NORMAL VAGINAL DELIVERY
HIE	HYPOXIC ISCHAEMIC ENCEPHALOPATHY
PLT	PLATELET
WB	WHOLE BLOOD
PC	PACKED CELL
FFP	FRESH FROZEN PLASMA
IVH	INTRAVENTRICULAR HEMMORHAGE

ABBREVIATION

ROP	RETINOPATHY OF PREMATURITY
GA	GESTATIONAL AGE
BW	BIRTH WEIGHT
ET-ROP	THE EARLY TREATMENT FOR RETINOPATHY OF PREMATURITY
RLF	RETROLENTAL FIBROPLASIA
CRYO-ROP	CRYOTHERAPY FOR RETINOPATHY OF PREMATURITY
LIGHT-ROP	THE EFFECT OF LIGHT REDUCTION ON RETINOPATHY OF PREMATURITY
VEGF	VASCULAR ENDOTHELIAL GROWTH FACTOR
IGF-1	INSULIN LIKE GROWTH FACTOR 1
CA	CHRONOLOGICAL AGE
PMA	POST MENSTRUAL AGE
NNF	NATIONAL NEONATOLOGY FORUM
ICROP	THE INTERNATIONAL CLASSIFICATION FOR RETINOPATHY OF PREMATURITY
AP-ROP	AGGRESSIVE POSTERIOR POLE RETINOPATHY OF PREMATURITY
PHPV	PERSISTANT HYPERPLASTIC PRIMARY VITREOUS
BEAT-ROP	BEVACIZUMAB ELIMINATES THE ANGIOGENIC THREAT OF RETINOPATHY OF PREMATURITY
RD	RETINAL DETACHMENT
PUFA	POLY UNSATURATED FATTY ACID
Epo	ERYTHROPOIETIN
WINROP	WEIGHT IGF-1 NEONATAL RETINOPATHY OF PREMATURITY

ETHICAL CLEARANCE LETTER

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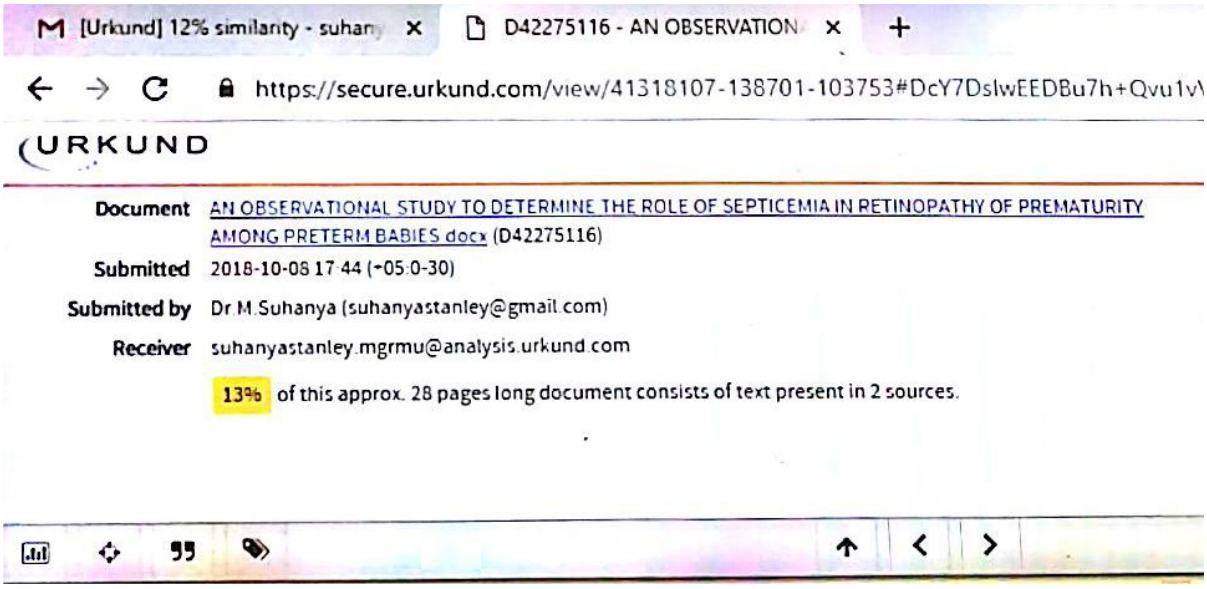
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